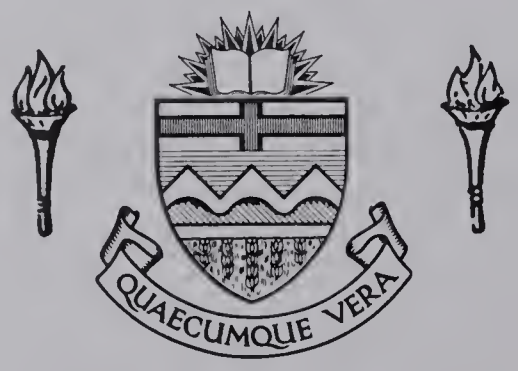

The University of Alberta
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Edmonton, Alberta

THE UNIVERSITY OF ALBERTA

SYNTHETIC STUDIES OF INDOLE ALKALOIDS

BY

SINING K. ANG, B.Sc.

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF MASTER OF SCIENCE

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

OCTOBER, 1967

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Synthetic Studies of Indole Alkaloids", submitted by Sining K. Ang in partial fulfilment of the requirements for the degree of Master of Science.

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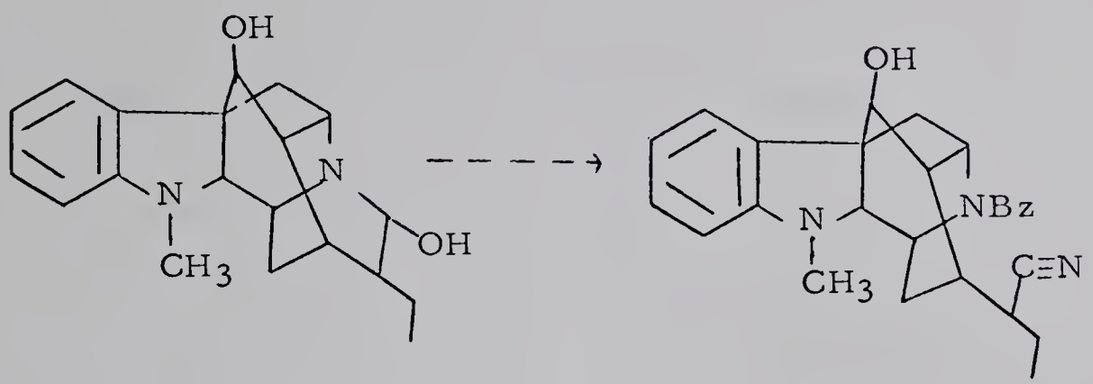
ABSTRACT

N-Benzoyl-anhydroajmalal oxime-A (19a) is the key intermediate in the total synthesis of ajmaline (1). 19a was prepared by degradation of 1 and its physical and chemical properties were studied.



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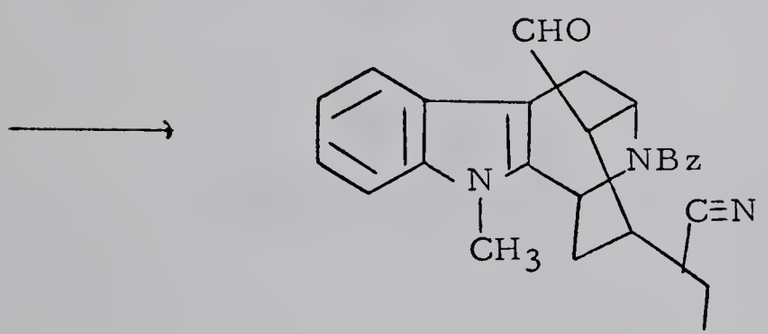
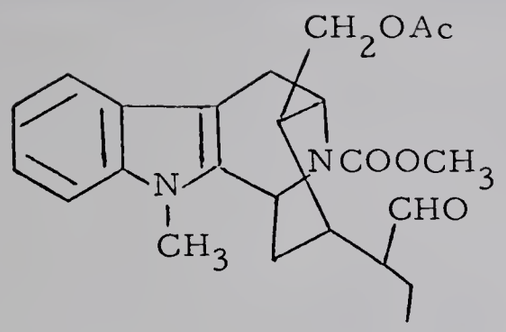


19a

One of the intermediates (68a) employed in the synthesis of ajmaline was converted to desmethylenemacroline (63a). 63a was also obtained by hydrolysis of macralstonin (62).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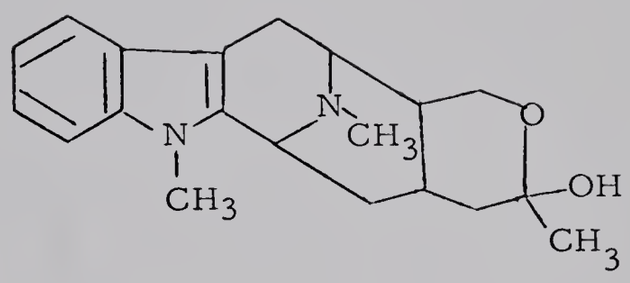
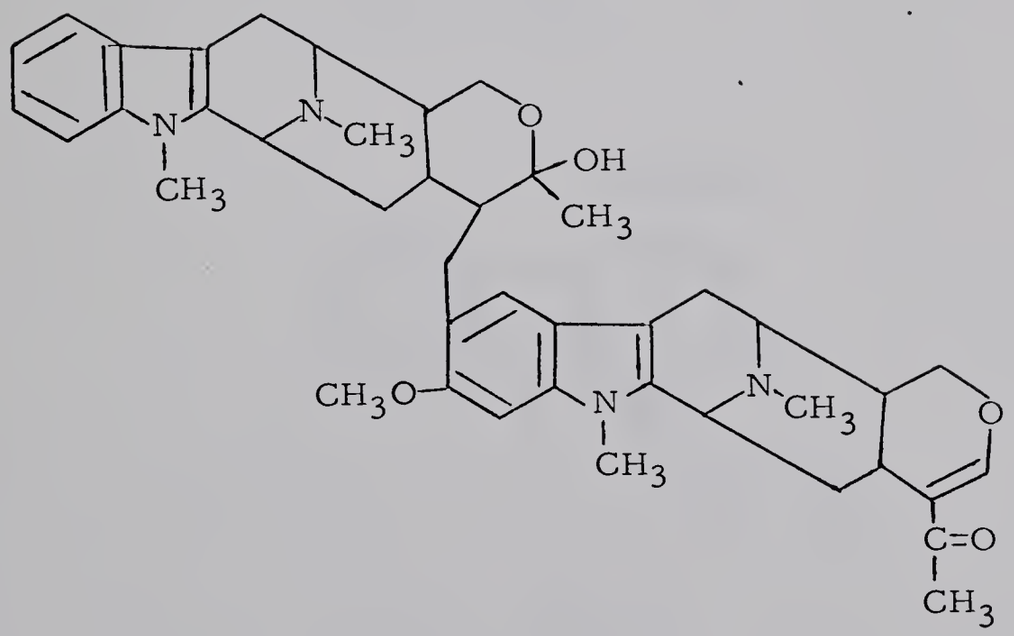
NCOOCH3
CHO
N
CH3

68a

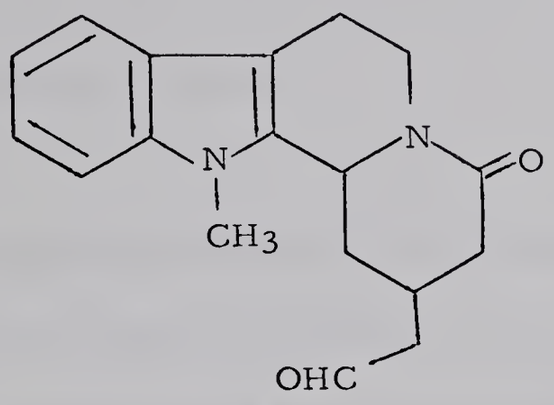

N
CH3
O
OH
CH3
N
CH3

63a

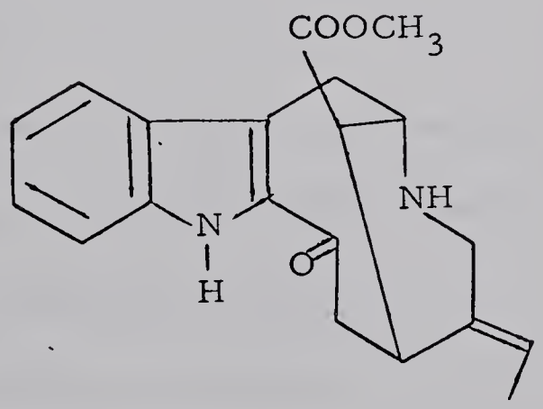

N
CH3
O
OH
CH3
N
CH3
CH3O
N
CH3
N
CH3
O
C=O
CH3

62

An attempt to synthesize vobasine (79), a 2-acylindole type alkaloid was unsuccessful. A new scheme was proposed and a potential intermediate (110) for the synthesis of 79 was prepared.



110



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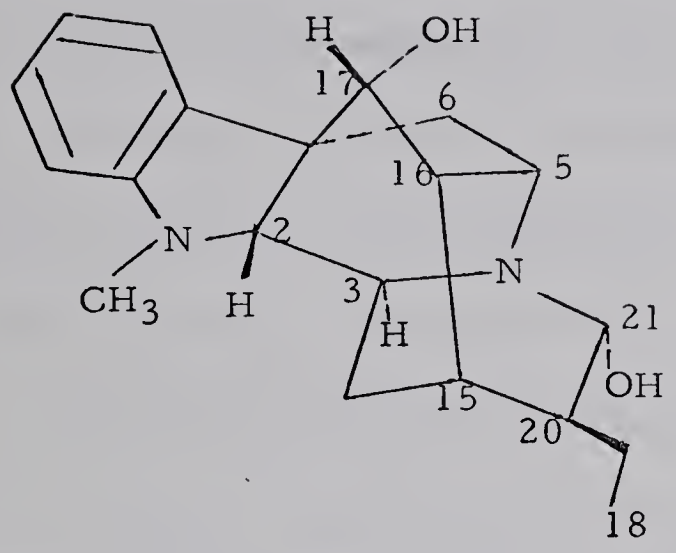
INTRODUCTION

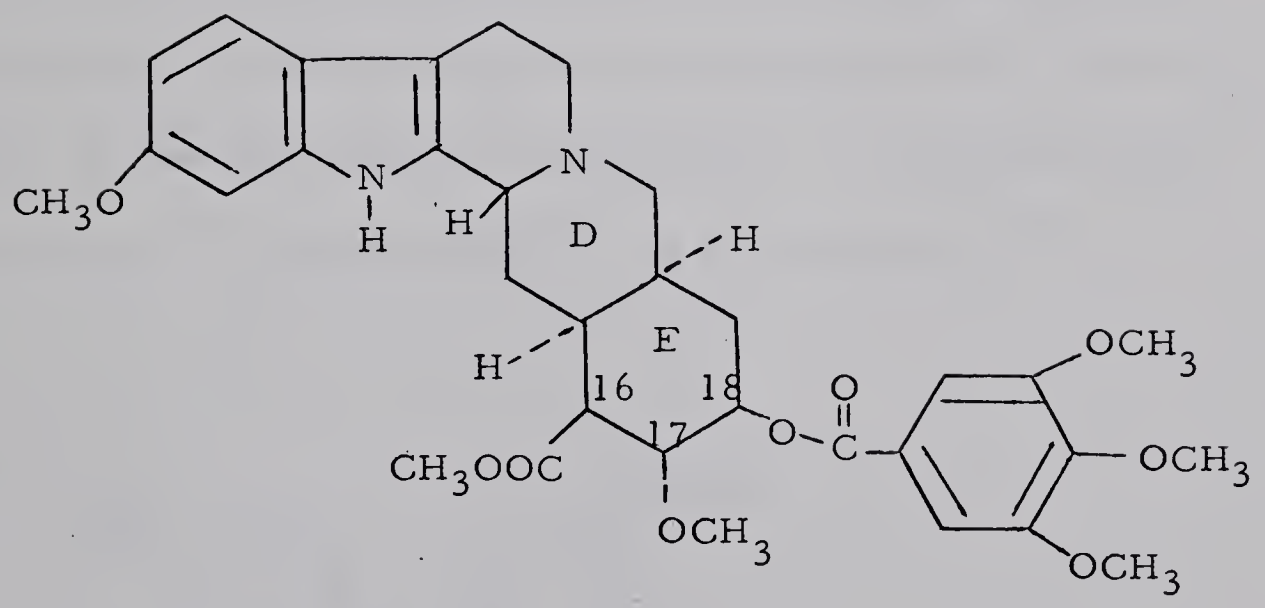
The study of indole alkaloids dates as far back as the era of classical organic chemistry. The progress made in this field, however, is comparatively recent, chiefly due to their structural complexity and the lack of means for elucidation in the past. Strychnine, for example, was intensively studied for sixty years before its structure was finally elucidated. Recent advances in natural products chemistry have been made possible with the invention of recording spectrometers. Structures of a large number of indole alkaloids were rapidly elucidated by use of infrared, nuclear magnetic resonance, ultraviolet and mass spectrometers and X-ray crystallography. The interest in these alkaloids was given a tremendous momentum by the discovery of their unique skeletal array and since then, some organic chemists have achieved some remarkable total syntheses. Among them were the total syntheses of strychnine (1954),[1] reserpine (1956),[2] yohimbine (1958),[3] ajmalicine (1961),[4] aspidospermine (1963),[5] and ibogamine (1965).[6]

Among the several hundred varieties of plants known to contain indole alkaloids, the Rauwolfia species received special attention. This was due to the isolation of reserpine from Rauwolfia serpentina Benth. of the family Apocynacae in 1952 and the recognition of its pharmacological significance as a sedative and hypotensive drug.

Actually, long before reserpine (2) was known, another and also the most abundant alkaloid present in R. serpentina, ajmaline (1), had been isolated by Siddiqui et al.[7] in 1931. However, little was known then about its chemistry. The interest in this compound was revived by


H
OH
17
6
16
5
N
2
N
CH3
H
3
H
21
OH
15
20
18

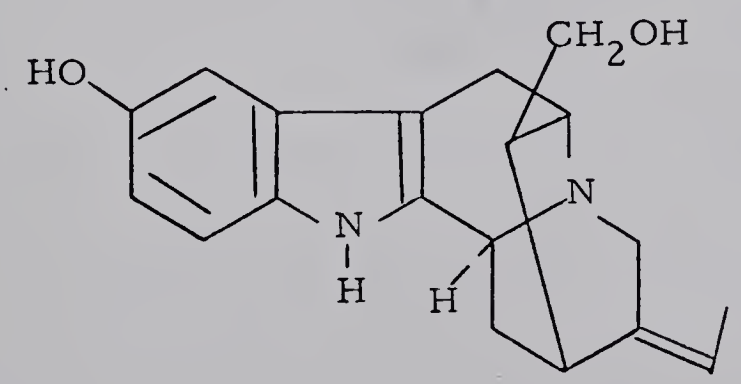
1


CH3O
N
H
N
H
D
H
H
E
16
18
17
O
C
OCH3
OCH3
OCH3
CH3OOC
OCH3

2

Sir Robert Robinson et al.[8] in 1954 at Oxford. After a series of extensive studies, the correct structure of ajmaline was advanced by Woodward[9] in 1956 at Harvard and accepted by Sir Robert Robinson in 1957. The stereochemistry of ajmaline has become the subject of discussion ever since its structure was known. Of the nine asymetric centers in the molecule of ajmaline, five of them were determined as a consequence of the existence of the molecule. The other four centers, namely, C_2, C_{17}, C_{20}, and C_{21}, assigned as shown in structure 1, were based on chemical evidence obtained by Taylor et al. at CIBA in 1961. This assignment was further confirmed by X-ray crystallographic analyses of two sarpagine derivatives, which were structurally related to ajmaline.

Following the determination of the structure of ajmaline, the structure of several other alkaloids isolated from the Rauwolfia and Vinca species were rapidly elucidated by interrelations with ajmaline derivatives. A few examples are sarpagine (3),[11] rauvomitine (4),[12] tetraphyllicine (5),[13] ajmalidine (6),[12] and sandwicine (7).[14]



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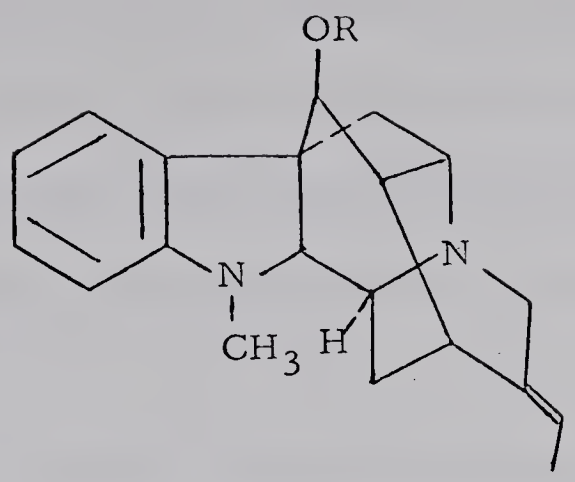
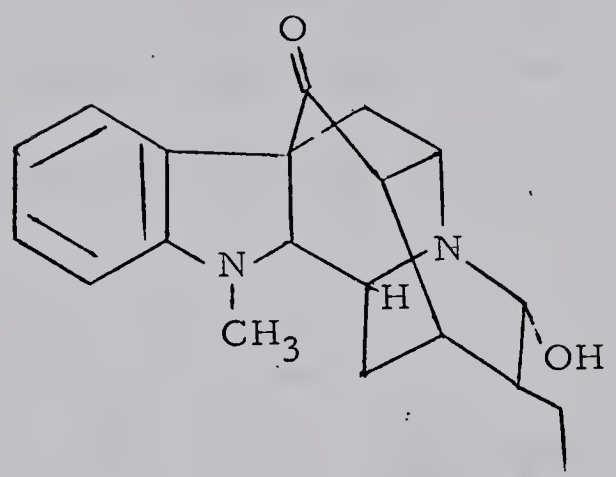


4 R = -COPh(OMe)$_3$

5 R = H



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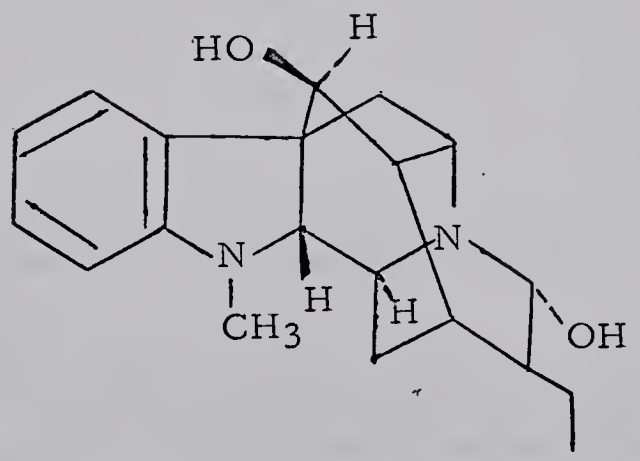
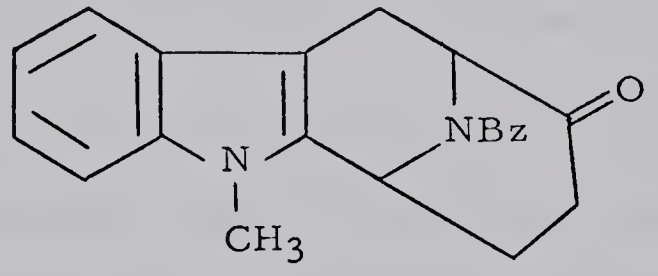


7

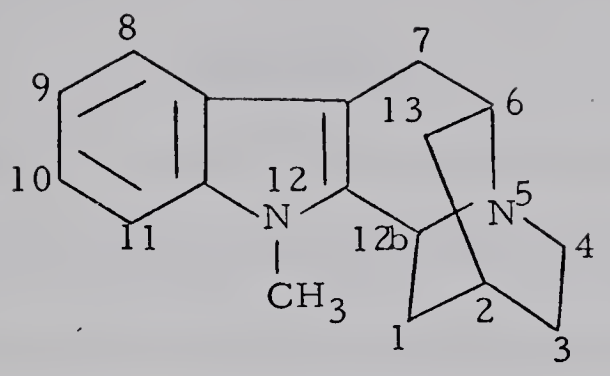
Biogenetically, sarpagine can be regarded as a derivative of a precursor of ajmaline. Thus, it was thought that a sarpagine-type compound could be an important intermediate towards the synthesis of ajmaline. (The biosyntheses of indole alkaloids are briefly discussed in the appendix.)

In 1963, an approach to the synthesis of ajmaline and sarpagine alkaloids was reported by Hobson and co-workers.[15] This approach involved the preparation of a tetracyclic ketone (8), as a potentially useful intermediate, in the expectation that further construction of the desired quinuclidine system would then be possible by several routes.



8

Then in 1965, Yoneda[16] reported the synthesis of another potential intermediate, 12-methyl-1,2,3,4,6,7,12,12b-octahydro-2,6-methano-indolo (2,3a) quinolizine (9). Compound 9 contains the fundamental skeleton of the sarpagine type alkaloids and introduction of suitable functional groups at C_3 and C_{13} would be necessary to complete a synthesis of ajmaline.



9

The first total synthesis of ajmaline has recently been completed in this laboratory. Part I of this thesis outlines the scheme employed in the synthesis and the portion of the synthesis which I have undertaken is discussed in detail. Part II is concerned with the description of an approach to synthesis of 2-acylindole type alkaloids.

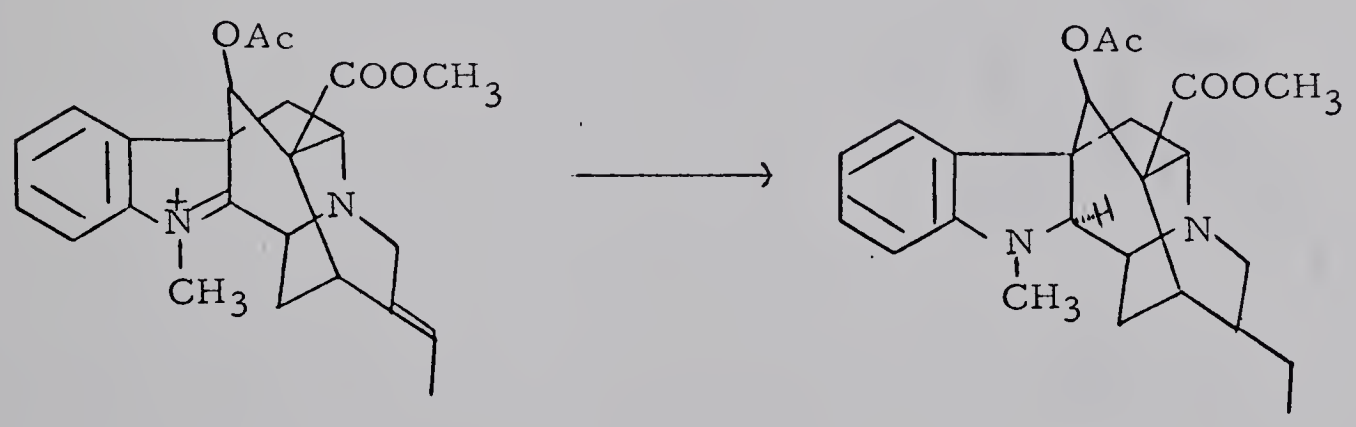
DISCUSSION

PART I - SYNTHETIC STUDIES OF AJMALINE

A - DEGRADATION OF AJMALINE TO THE KEY INTERMEDIATE 19a

GENERAL

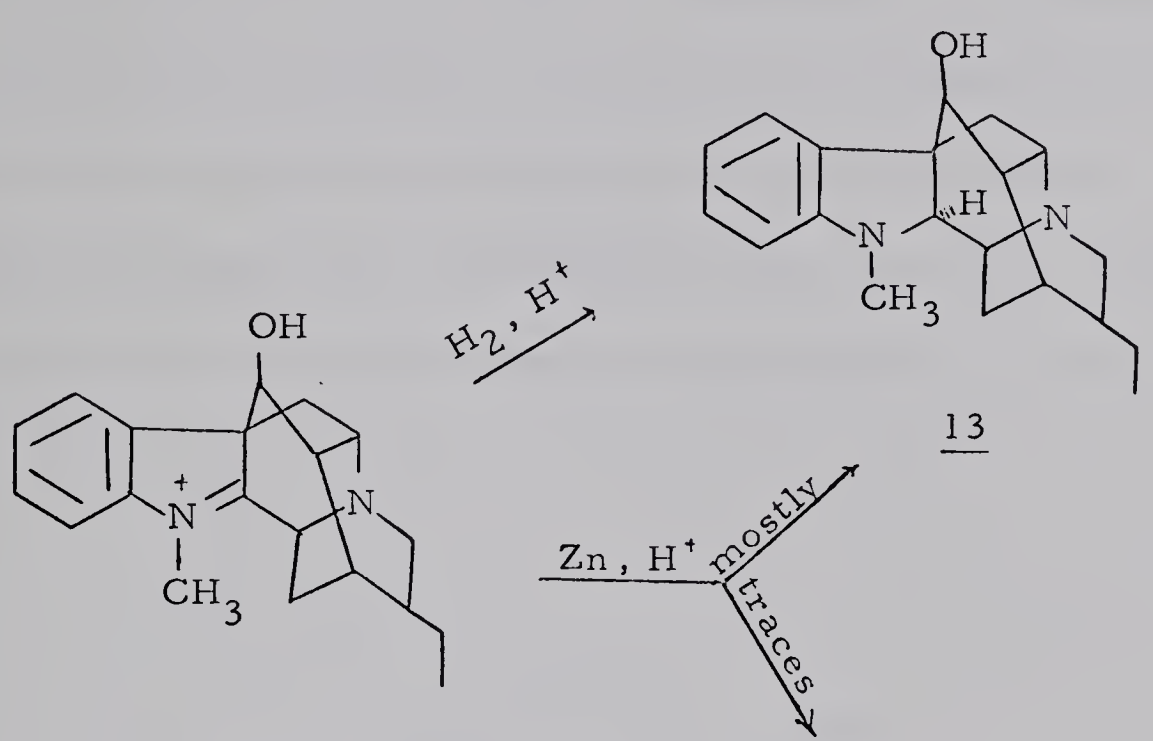
In order to achieve an efficient route toward the synthesis of ajmaline, the stereoselective introduction of the two asymetric centers, namely, C_2 and C_{17} into synthetic intermediates was studied. The introduction of the C_2 center presumably at the last stage of the total synthesis was first examined. Janot et al.[17] reported that catalytic hydrogenation of compound (10) in acid medium provided exclusively dihydrovincamedine (11), whose stereochemistry at C_2 was epi as shown in 11, whereas ajmaline possesses the normal configuration at



10 11

this center. Taylor et al.[18] also reported analogous observations.

On catalytic hydrogenation of the indolenine (12) in hydrochloric acid they obtained 2-epi-deoxyajmaline (13) in quantitative yield. Reduction of 12 with zinc dust provided traces of deoxyajmaline (14) in addition to 13.



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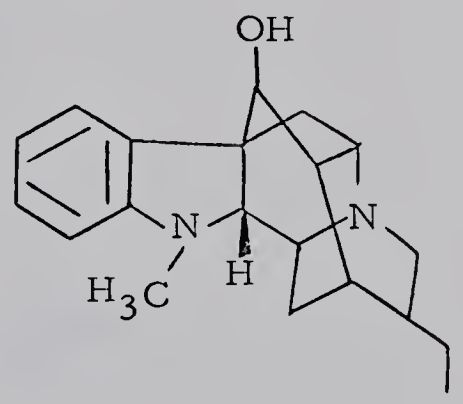
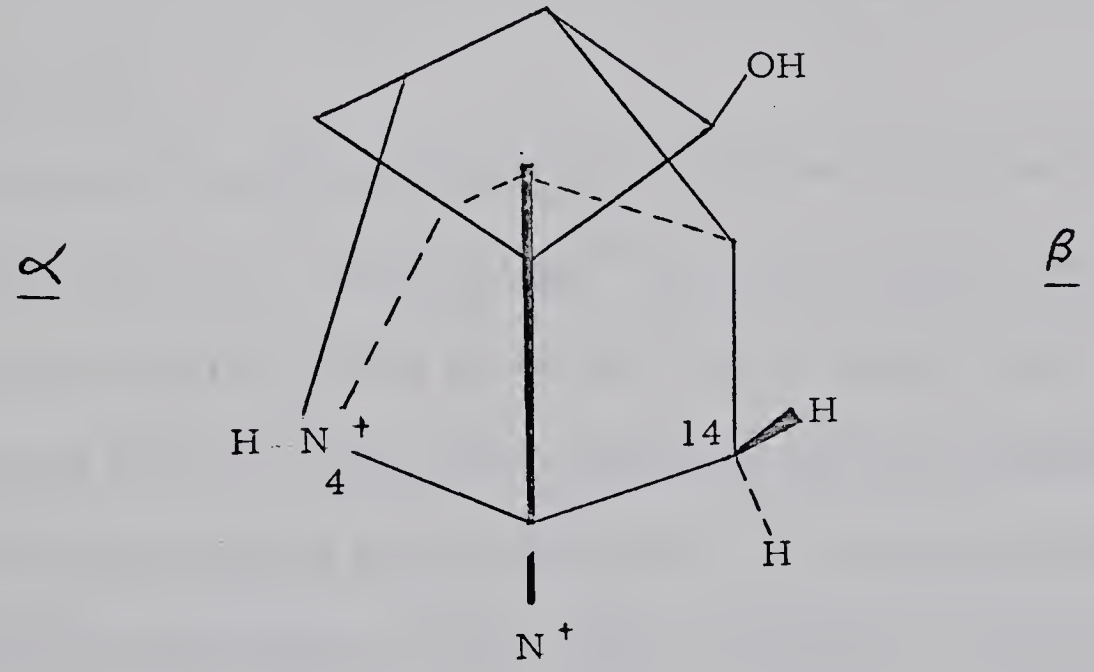


14

S. Masamune[23] interpreted these results in the following fashion. A study of a Drieding model of 12 (a side view of 12 is shown in formula 15) showed that there was only a slight difference in steric hindrance between the α and β sides of the molecule toward attack by

the reagent at C_2. Furthermore, N. Nakatsuka[23] proved that when both deoxyajmaline 14 and 2-epi-deoxyajmaline 13 were subjected to hydrogenation conditions no isomerization was observed. Therefore, the formation of the epi-compounds in the cases reported above was rather surprising, if steric hindrance is the deciding factor. S. Masamune then assumed that the exclusive α attack in the reported cases was due to the presence of the protonated nitrogen atom on the α side. Thus, by neutralizing the charge, vis., benzoylation of N_b (as shown in Formula 16) and at the same time increasing the steric hindrance on the α



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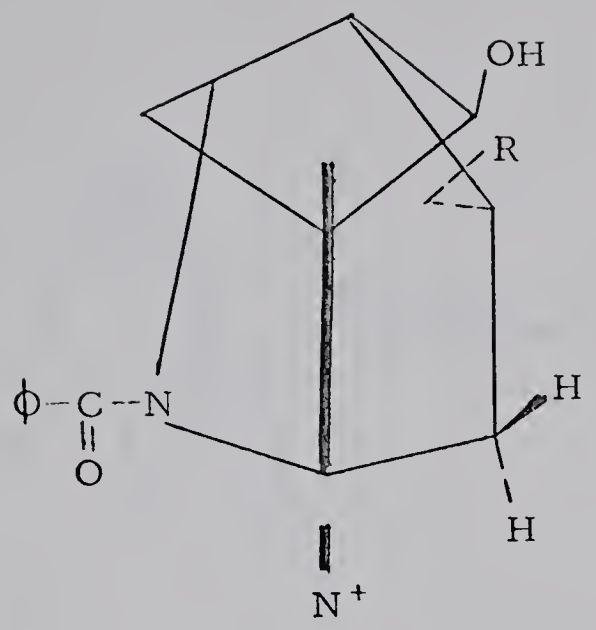
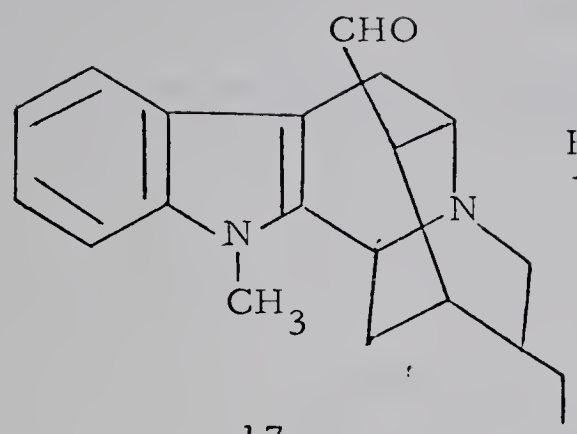


α β

16

side of the molecule, an ajmaline-type compound with the desired stereochemistry at C_2 may be obtained. Therefore, the first requirement of the key intermediate in the synthesis of ajmaline was to possess a benzoyl group at N_b.

The presumably penultimate step in the synthesis of ajmaline would involve cyclization at C_7. Taylor et al.[18] have achieved cyclization of 21-deoxyajmalal-A (17) (A refers to the less stable isomer where the functional group at C_{16} is endo with respect to the indole nucleus) in acid medium affording compound (18), in which the acetoxy group possessed the required stereochemistry at C_{17}. This cyclization was effected by taking advantage of the vicinal location of the nucleophilic β-position of the indole nucleus and the electrophilic aldehyde group to form the hexacyclic ring system. In accord with this view, 21-deoxyajmalal-B (17a) (B refers to the more stable isomer where the functional group at C_{16} is exo with respect to the indole nucleus) was not cyclized under the same



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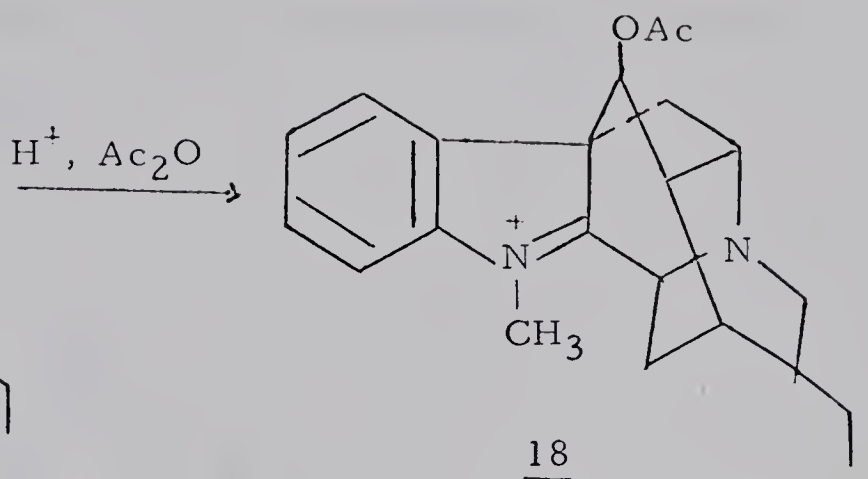

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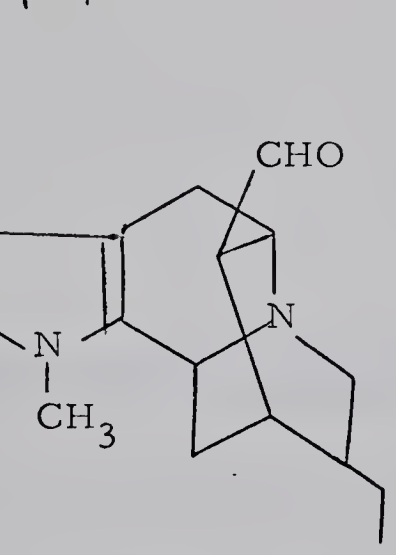
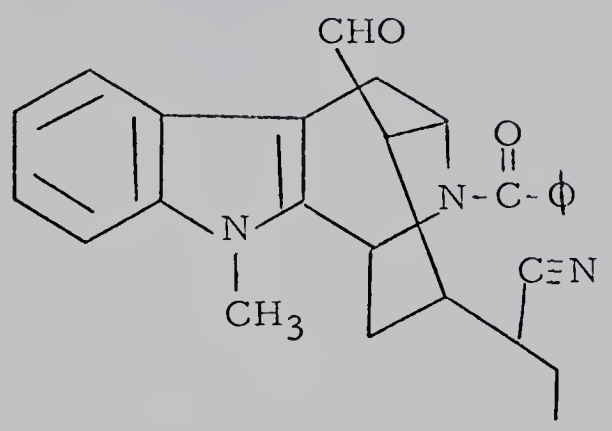


17a

conditions, since the B-isomer 17a could not be converted to the A-isomer. In summary, the second requirement of the key intermediate was to possess an aldehyde group at C_{16} with A-configuration.

The above mentioned requirements were satisfied in the proposed

key intermediate (19a) which possesses the potential ajmaline skeleton. The C≡N group was chosen for the following reasons: (1) it would not readily react with the aldehyde group at C_{16} in acid medium, (2) it would be convertible to an aldehyde group.

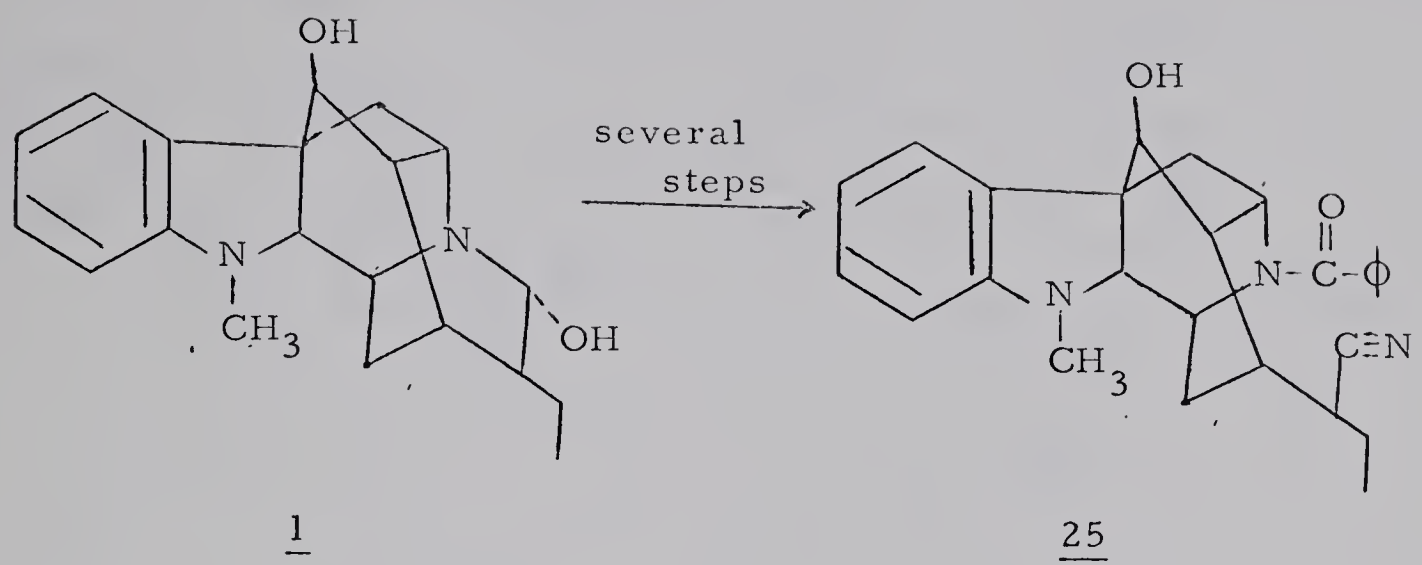


19a

OUTLINE OF SYNTHETIC SCHEME

The synthesis of ajmaline is now divided into three parts, namely; (1) degradation of ajmaline to a key intermediate, (2) conversion of the key intermediate to ajmaline, (3) preparation of the synthetic key intermediate and if necessary conversion of the synthetic intermediate to ajmaline.

The first part of the synthesis is discussed in detail below. There were two schemes proposed for degradation of ajmaline to a key intermediate. Scheme A involved initial cleavage of N_b-C_{21} bond, followed by lead tetraacetate cleavage of the cyclopentane ring (C_7-C_{17} bond).



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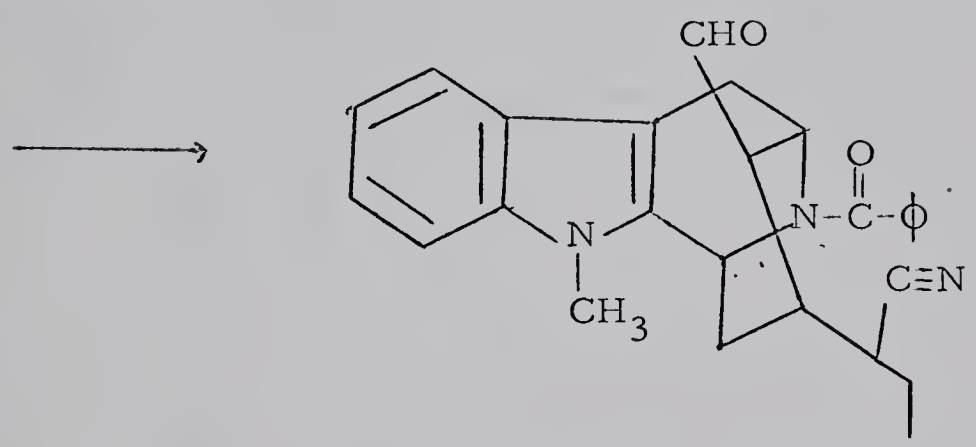
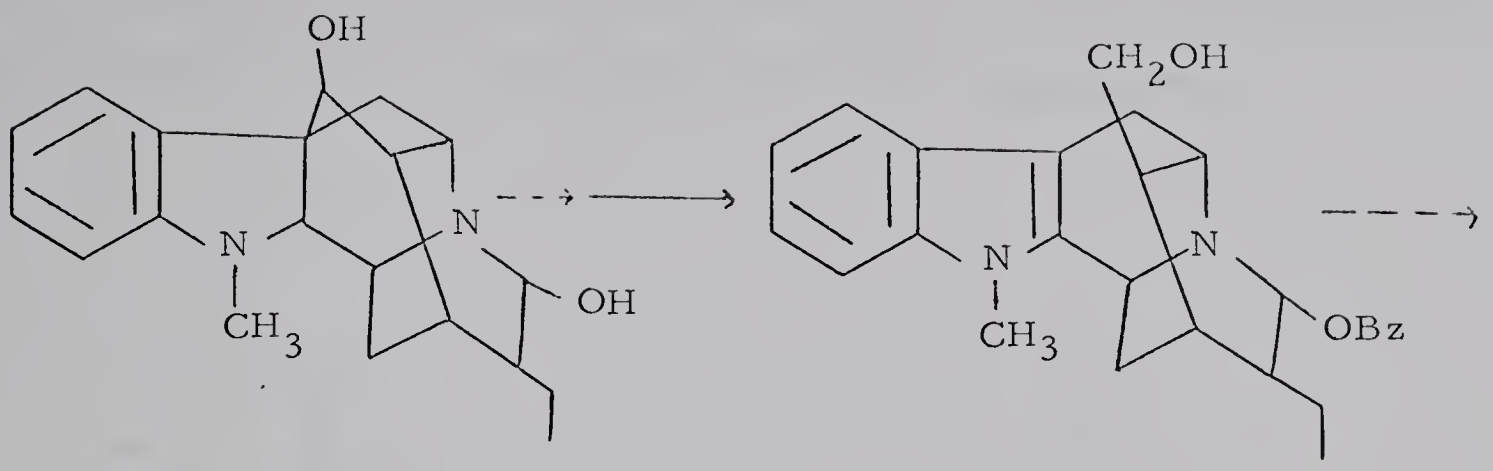


19a

SCHEME A

Scheme B was the reverse of the first method and involved initial C_7-C_{17} bond cleavage followed by cleavage of N_b-C_{21} bond.



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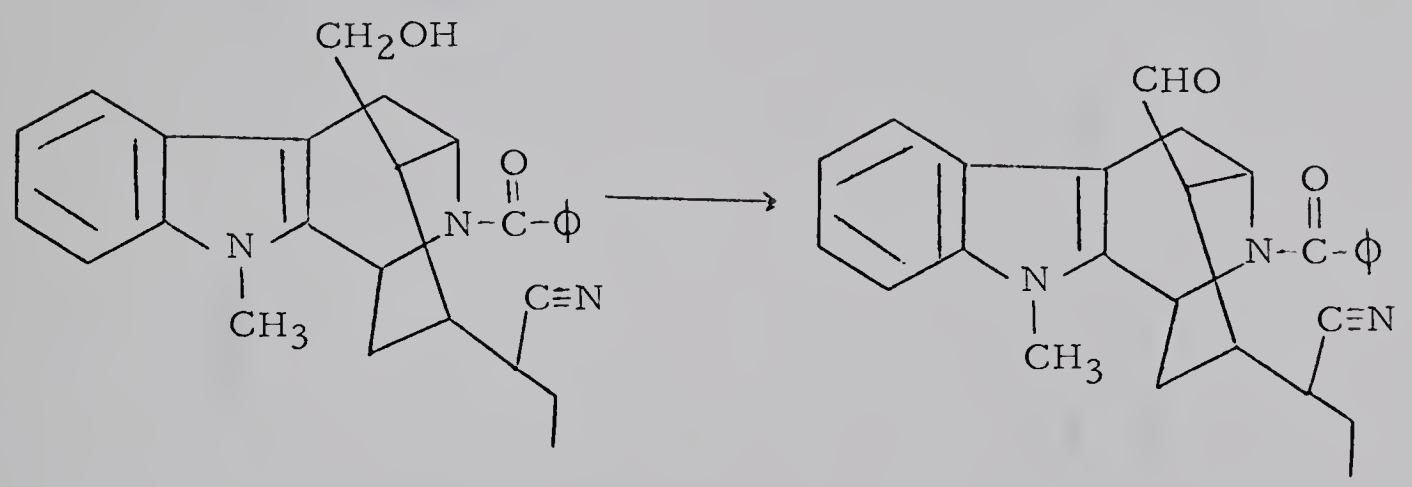


42 19a

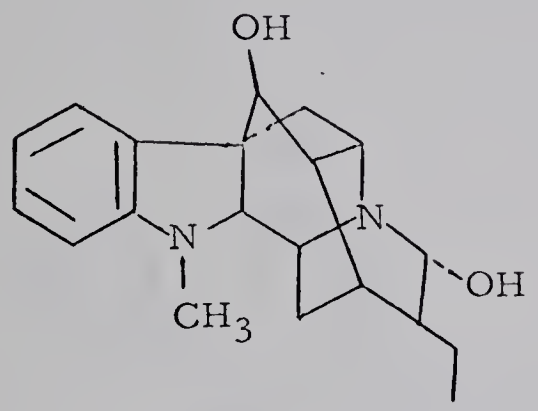
SCHEME B

SCHEME A

1 - PREPARATION OF 25

Cleavage of the carbinolamine system of ajmaline has been reported in the literature[8] by three methods, two of which seemed applicable to our case. The first method involved the formation of ajmaline methiodide (20) which is in equilibrium with (21). However, the presence of N_b-CH_3 group in 21 is not desirable since it would be difficult to convert N_b-CH_3 to N-Bz. To avoid this, an attempt was made to prepare the ketal

of the masked aldehyde group of ajmaline. However, this approach was unsuccessful. The experimental details of this approach is discussed in the appendix. The second method involved the prepartion of



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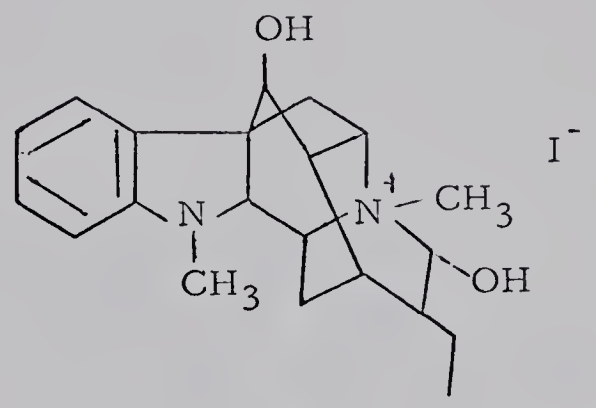

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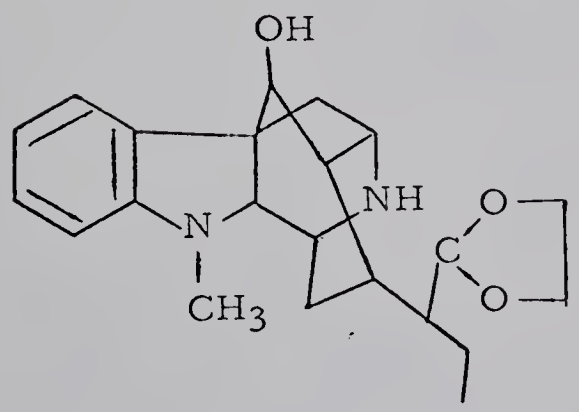

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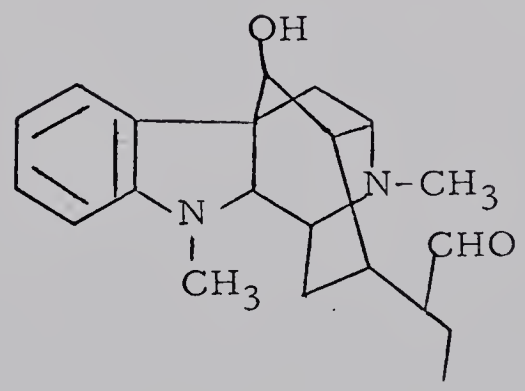
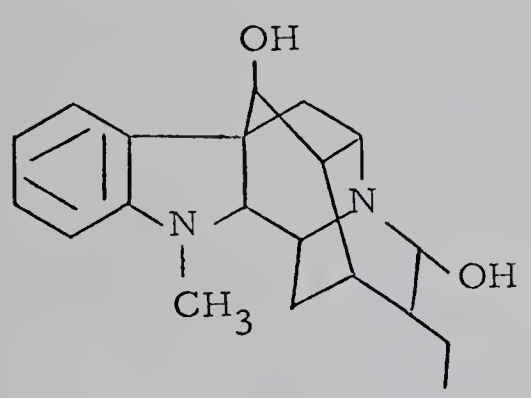
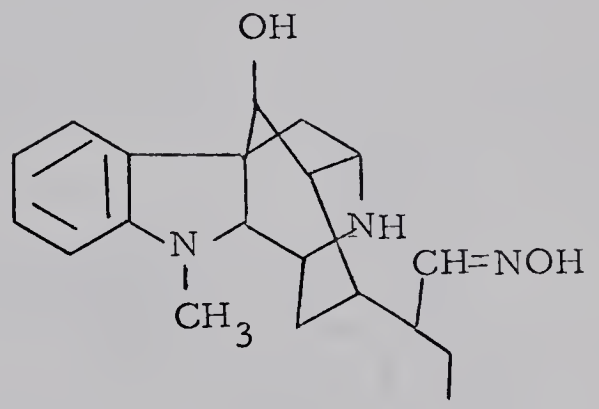


21

anhydroajmaline oxime (24) from ajmaline 1 in two steps.[8] Benzoylation of 24 provided in quantitative yield anhydro-N_b-benzoyl-ajmaline oxime (25), whose infrared spectrum showed absorptions attributed to hydroxyl (3330 cm^{-1}), nitrile (2230 cm^{-1}) and amide carbonyl (1620 cm^{-1}).



1



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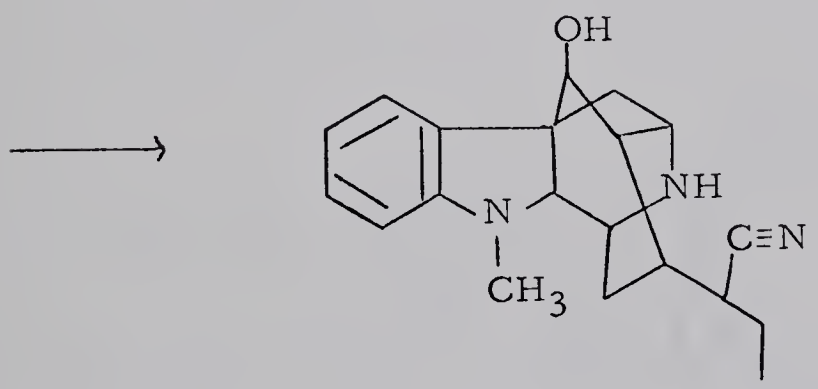
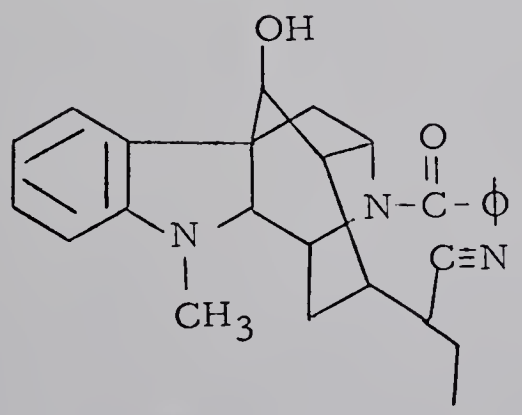


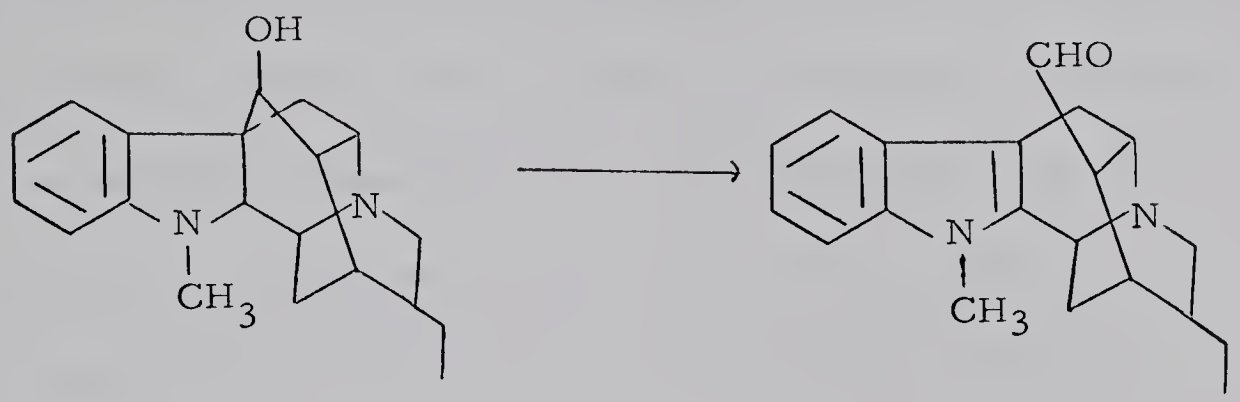
24



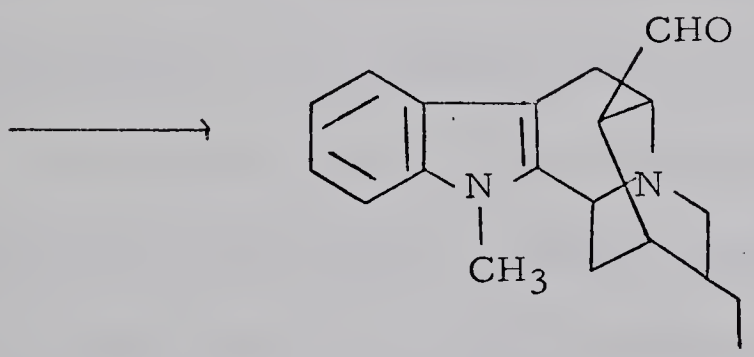
25

2 - LEAD TETRAACETATE OXIDATION OF 25

In 1956 Schenker and Woodward[9] reported the formation of an indole aldehyde by lead tetraacetate oxidation of deoxyajmaline 14. Later in 1961, Taylor et al.[10] isolated deoxyajmalal-A 17 in high yield and 17 could be quantitatively converted with alkali to 17a, which was identical with the aldehyde reported by Schenker and Woodward.



1 17

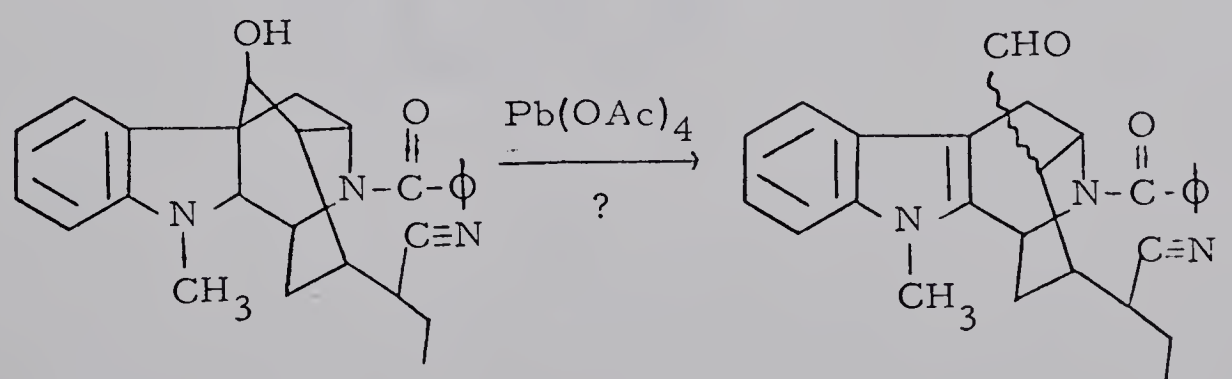


17a

Since the conventional work-up procedure for a lead tetraacetate oxidation was tedious, a more convenient procedure introduced by Schmid et al.[19] was adopted. This consisted of filtering the reaction

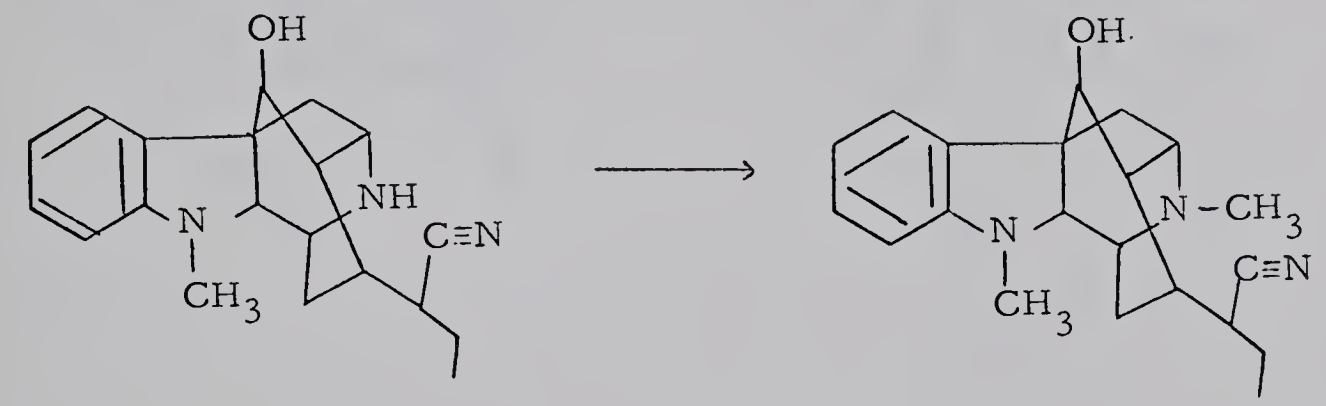
mixture through neutral alumina and eluting of the materials by suitable solvents. The corresponding aldehyde product was thought to be stable on neutral alumina since no epimerization was observed in the case of benzoylajmalal (32) (vide infra).

Oxidation of 25 with lead tetraacetate and work-up by Schmid's procedure gave an amorphous material whose infrared spectrum showed bands attributed to aldehyde (2700, 1725 cm^{-1}) and nitrile (2225 cm^{-1}). However, the nmr spectrum at room temperature suggested the absence of N_a-CH_3 (no sharp singlet around τ 6.4) and the aldehyde resonance absorption was very broad (see figure 5). These data from the nmr spectrum and the fact that 19 could not be induced to crystallize, led us to believe that 19 was not obtained or at least not in reasonably pure form. It was then suspected that oxidative demethylation might have taken place.[20] Since in all the reported cases, vis., deoxyajmaline $\longrightarrow$ deoxyajmalal, the compound subjected to oxidation possessed basic nitrogen, the failure to obtain 19 was thought to be due to compound 25 being neutral for some reason. However, addition of triethylamine (one molar equivalent) to the reaction mixture of 25 with lead tetraacetate did not alter the result.

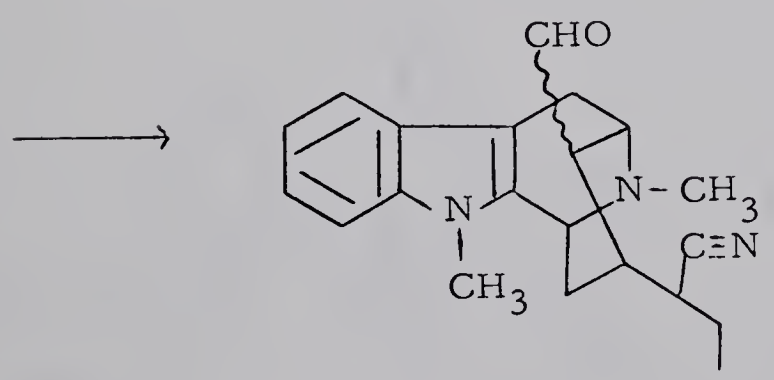


25 19

In view of the above results, a basic compound (26) was prepared by methylation of 24. The nmr spectrum of 26 showed resonance absorptions attributed to N-CH_3 protons at τ 7.34 and 7.54. Oxidation of 26 with lead tetraacetate and work-up by Schmid's procedure afforded anhydro-N_b-methylajmalal oxime (27) whose infrared spectrum showed absorptions attributed to aldehyde (2700, 1725 cm^{-1}) and nitrile (2225 cm^{-1}). The nmr spectrum showed absorptions at τ 0.33 (doublet, C<u>H</u>O), 6.4 (singlet, N_a-C<u>H</u>$_3$) and 7.58 (singlet, N_b-C<u>H</u>$_3$). However, the stereochemistry at C_{16} of 27 was not determined.



24 26

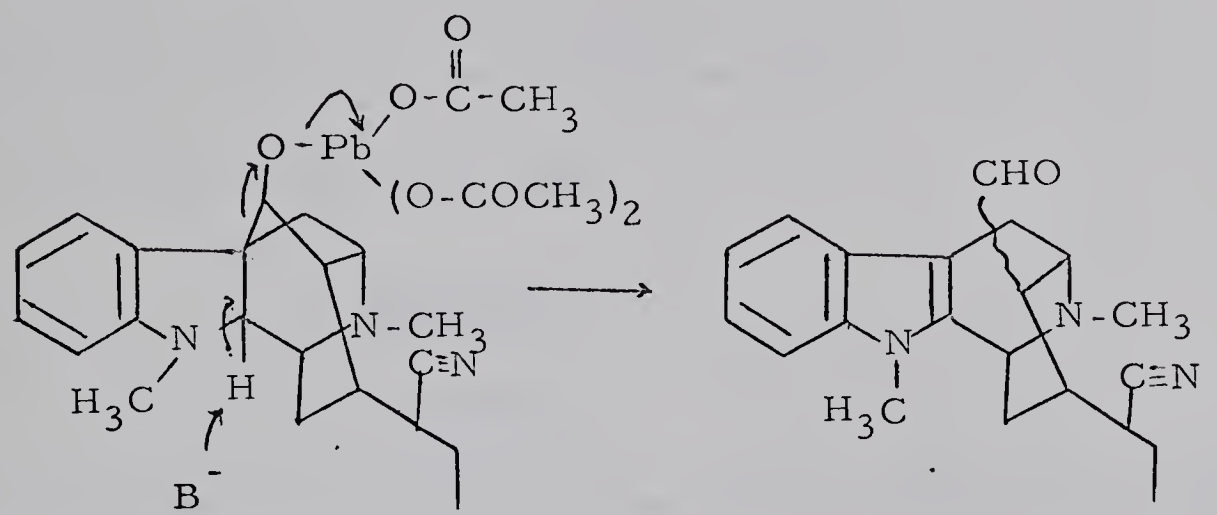


27

3. MECHANISM OF LEAD TETRAACETATE OXIDATION

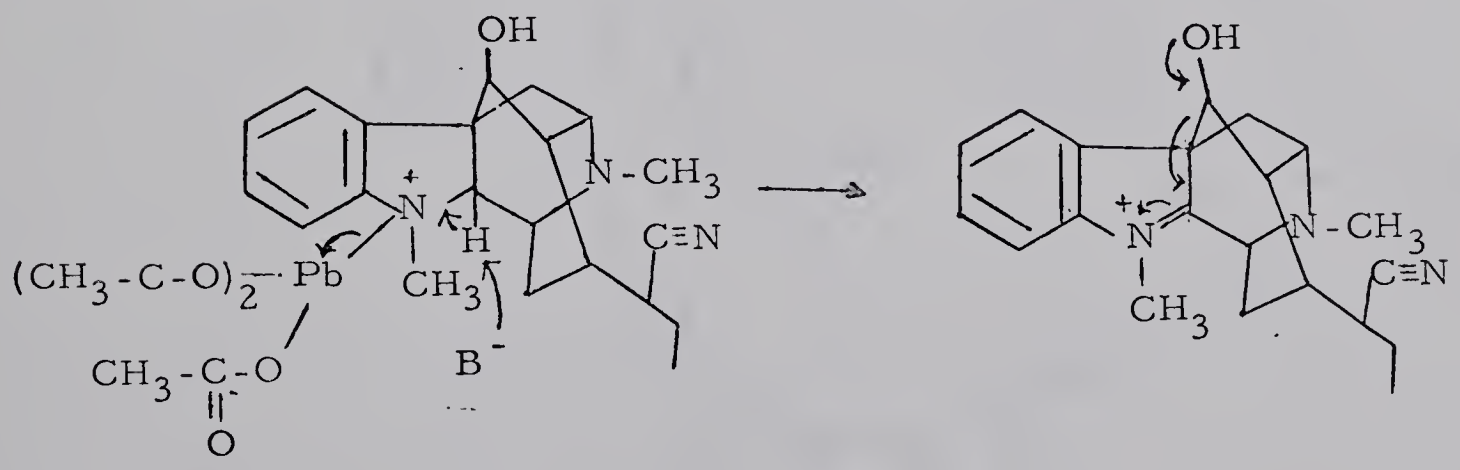
Lead tetraacetate oxidations are thought to be initiated by the ester or salt formation with a hydroxyl or amino group followed by the electron transfer as indicated below.[20]

(1)



28 27

(2)



29 30

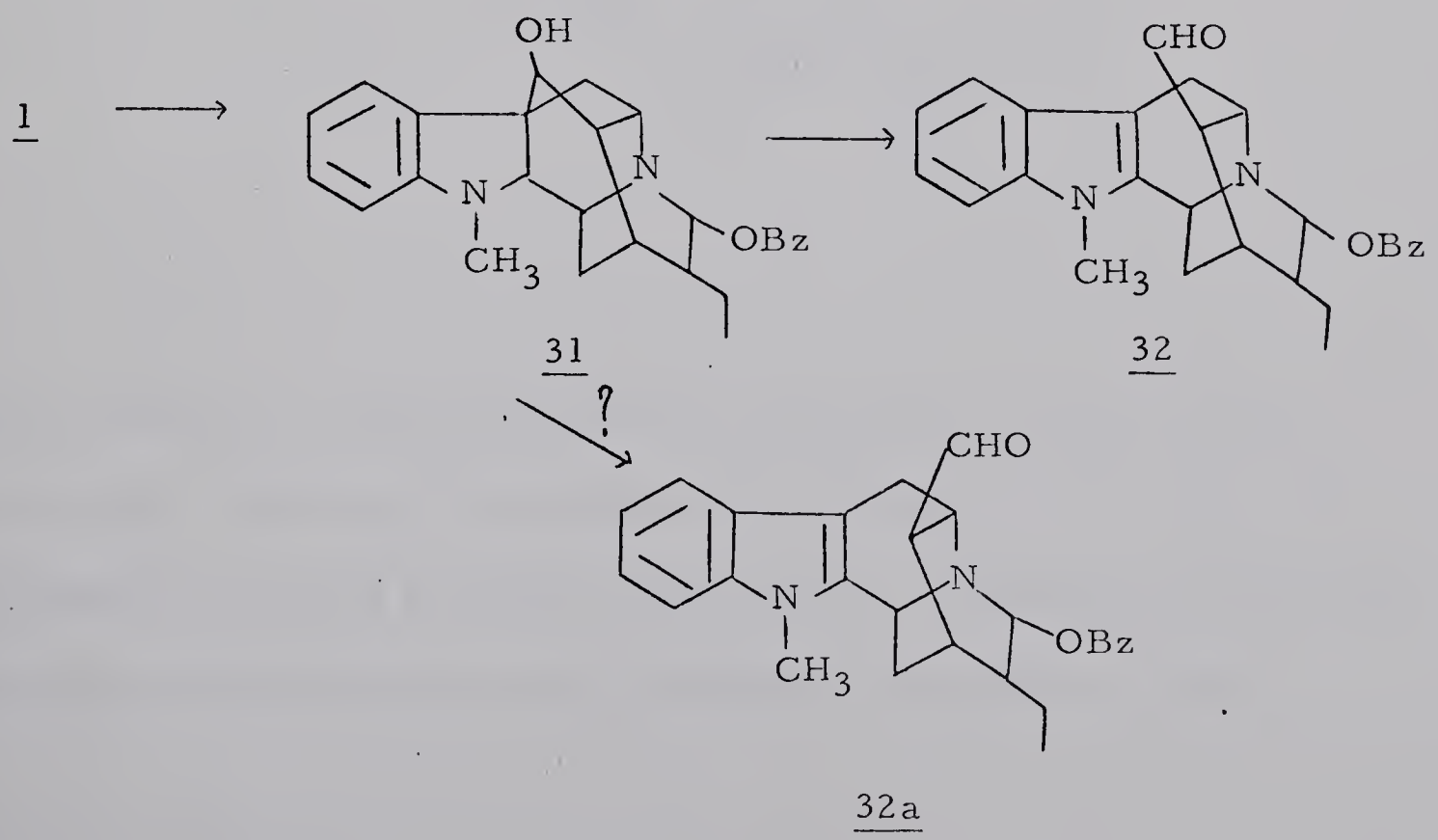
4 - INTERPRETATION OF RESULTS

The absence of N_a-CH_3 protons in the nmr spectrum of 19 was interpreted as a result of demethylation at N_a position of compound 25. This was conceivable if the hydroxyl group of 25 was protected with a functional group such as an acetate and a large excess of lead tetra-acetate was present. However, under the reaction conditions used, there is no obvious reason why demethylation should occur in 25. These seemingly inconsistent results will be explained from data obtained at the later stage of this work.

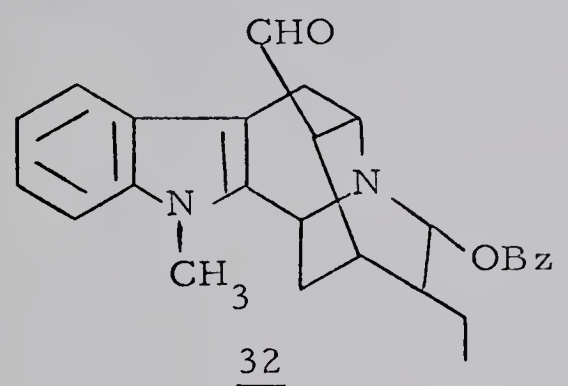
SCHEME B

1 - GENERAL

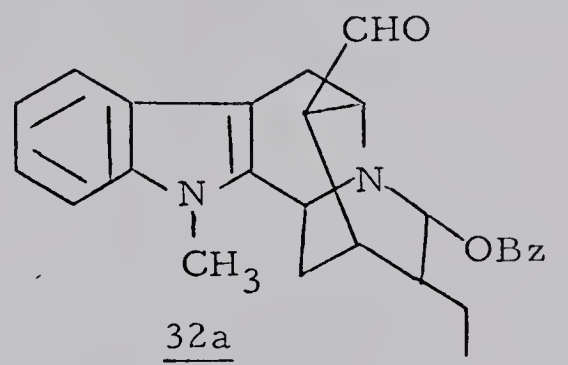
Cleavage of the C_7-C_{17} linkage of an ajmaline derivative by lead tetraacetate has been reported by Schmid et al.[19] They obtained the aldehyde (32a) exclusively on oxidation of benzoylajmaline 31 with lead tetraacetate. With this in mind, attempts were made to isolate the



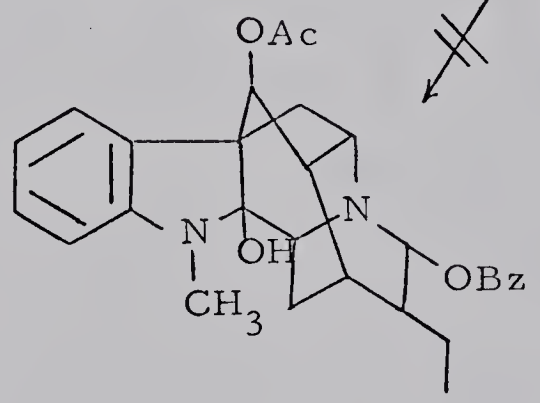
A-epimer (32) by changing the reaction condition, vis., change of solvent and work-up procedure. All attempts produced only one product which was believed to be 32a. These results were unfavorable for our purposes since the A-epimer 32 was the desired compound. However, Y. Yasunari proved that Schmid's compound was not 32a, but in fact was the desired A-epimer 32. This assignment was based on the experiment that treatment of the product from lead tetraacetate oxidation of 31 with acetic anhydride, acetic acid and hydrogen chloride afforded the cyclized compound (33),[23] while 32a would not be expected to cyclize under the



32

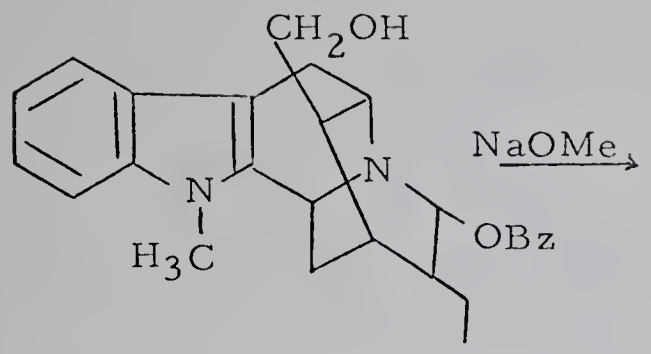


32a

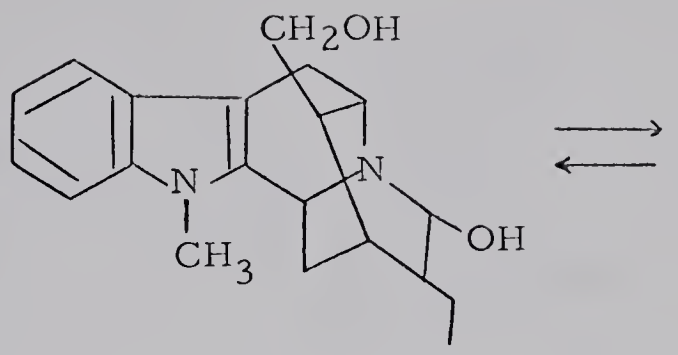


33

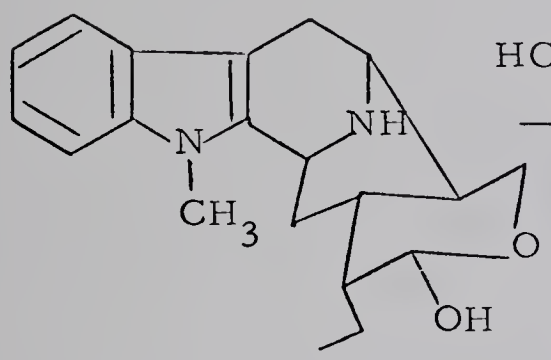
reaction conditions. Reduction of 32 with sodium borohydride afforded A-alcohol (34). Cleavage of the carbinolamine linkage of alcohol 34 was accomplished as outlined in Scheme I (see page 23). Hydrolysis of benzoate 34 with sodium methoxide liberated a compound in the form of either a



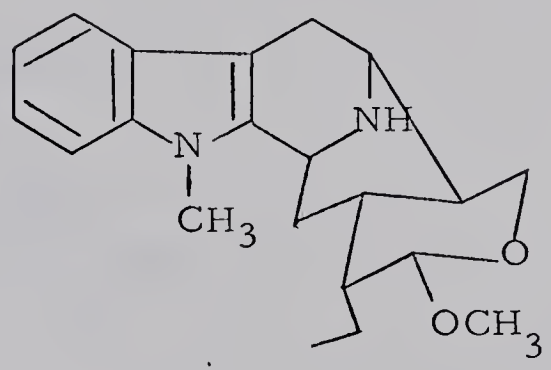
NaOMe



34 35

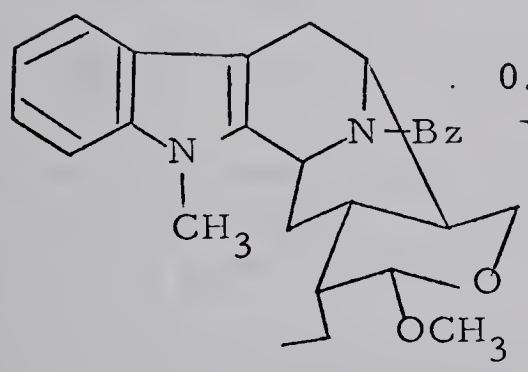


HCl, MeOH

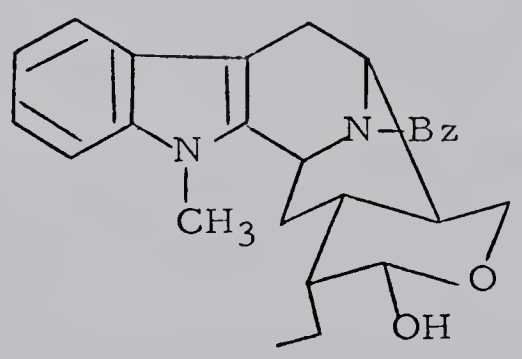


ϕ-COCl

36 37



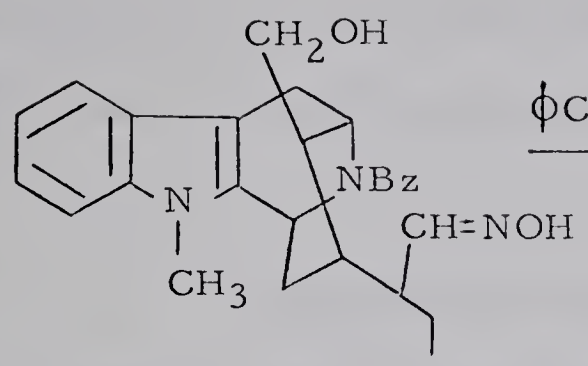
0.5N HCl



$H_2NOH \cdot HCl$

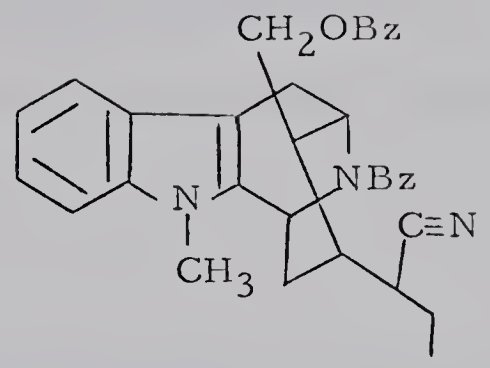
38 39

SCHEME I

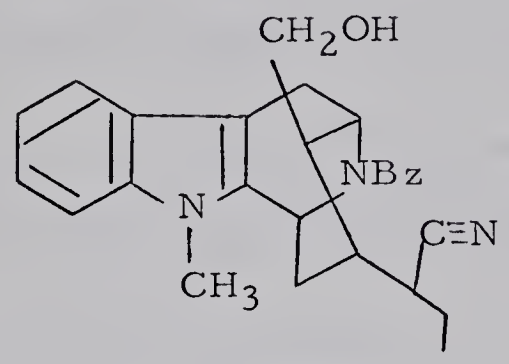


40

ϕCOCl

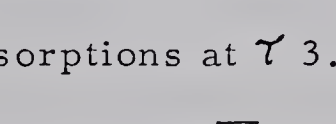
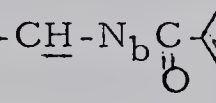


41



42

SCHEME I CONT'D

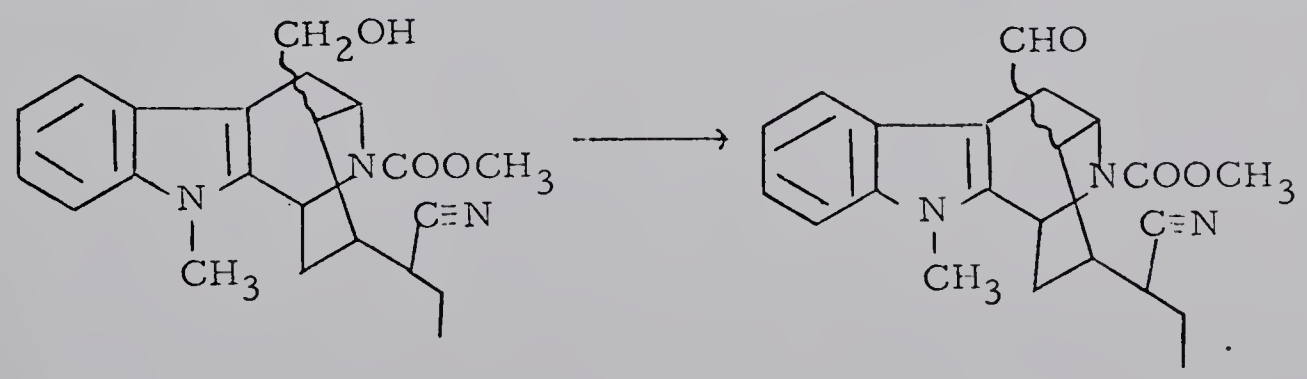
carbinolamine (35) or hemiacetal (36). With methanolic hydrochloric acid, the equilibrium is shifted to the hemiacetal 36 because 36 is subsequently methylated with methanol. Benzoylation followed by mild hydrolysis provided the N_b-benzoyl hemiacetal (39) whose nmr spectrum showed resonance absorptions at τ 3.9 (broad singlet, ), 4.95 (broad singlet, ), 5.9 (-C=C-C$\underline{H}_2$-CH-), 6.32 (broad singlet, N_a-C$\underline{H}_3$). Taking advantage of the potential aldehyde in 39 an oxime derivative (40) was prepared and dehydration of the aldoxime 40 with benzoyl chloride and pyridine gave the nitrile (41) in quantitative yield. Hydrolysis of 41 with sodium methoxide gave in 88% yield the alcohol (42) whose infrared spectrum showed absorptions

attributed to alcohol (3580, 3350 cm^{-1}), nitrile (2230 cm^{-1}) and amide carbonyl (1620 cm^{-1}). The critical step involving oxidation of the alcohol 42 to the corresponding aldehyde 19 is discussed in the following section.

2- OXIDATION OF 42

In 1965, Moffat et al.[21] reported the development of an efficient and extremely mild method for the oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones. This method involves the reaction at room temperature of an alcohol with dimethylsulfoxide (DMSO), dicyclohexylcarbodiimide (DCC) in the presence of a proton source such as anhydrous phosphoric acid or pyridinium trifluoroacetate. The reaction has recently been applied with considerable success by a number of workers. Albright and Goldman[22] reported another novel method of oxidation of alcohols to the corresponding carbonyl derivatives with DMSO and certain acid anhydrides.

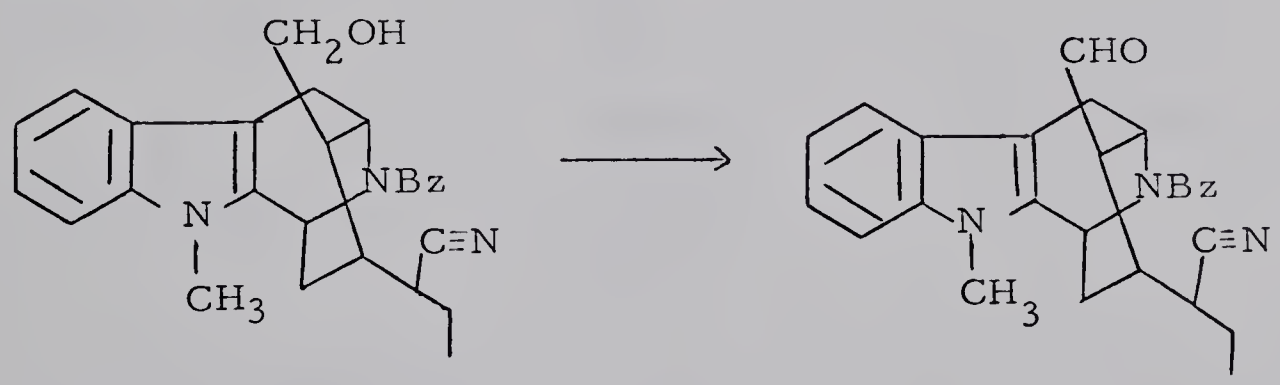
Compound 46 happened to be available to us and was used as a model compound for this oxidation. (We prepared 46 for some other purpose and is discussed in the appendix.) Reaction of 46 with DMSO containing DCC and pyridinium trifluoroacetate afforded aldehyde (47) in 70% yield (after chromatography on alumina). A similar result was obtained when



46 47

46 was oxidized with DMSO and acetic anhydride. The infrared spectrum of 47 showed absorptions attributed to aldehyde (2700, 1725 cm^{-1}), nitrile (2230 cm^{-1}) and amide carbonyl (1695 cm^{-1}) groupings. The nmr spectrum showed absorptions at τ 1.25 (doublet, C<u>H</u>O), 6.32 (singlet, N_a-C<u>H</u>$_3$) and 6.25 (singlet, -OC<u>H</u>$_3$).

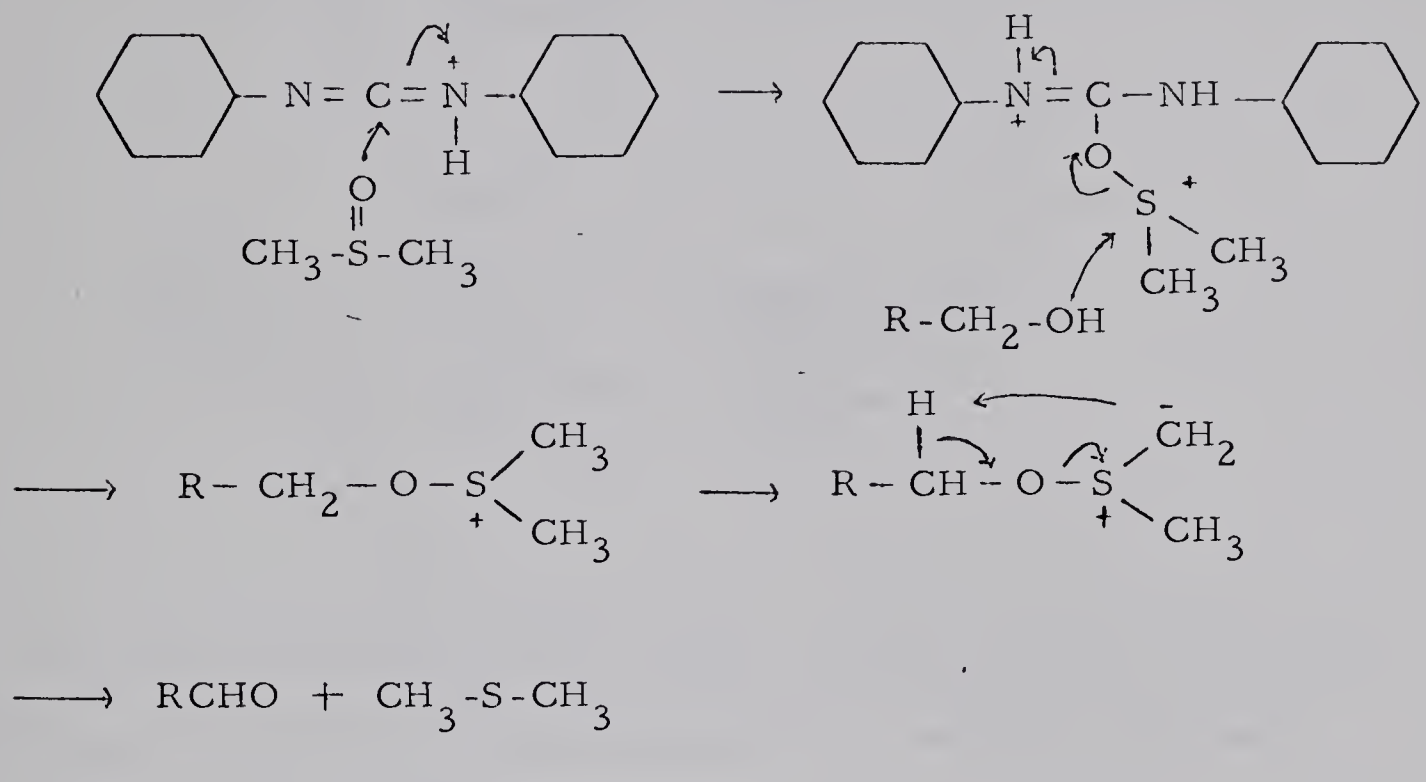
Since the DMSO oxidation was applied successfully to model compound 46, there was little doubt that it should go smoothly for the compound 42. Oxidation of 42 (see Scheme I) with DMSO and acetic anhydride afforded amorphous material which was chromatographed over silicic acid. To our surprise, the nmr spectrum of this material showed very broad N-C<u>H</u>$_3$ and C<u>H</u>O absorptions similar to those of the product obtained by lead tetraacetate oxidation of 25, while the infrared spectrum showed absorptions attributed to C<u>H</u>O group (see figure 7).



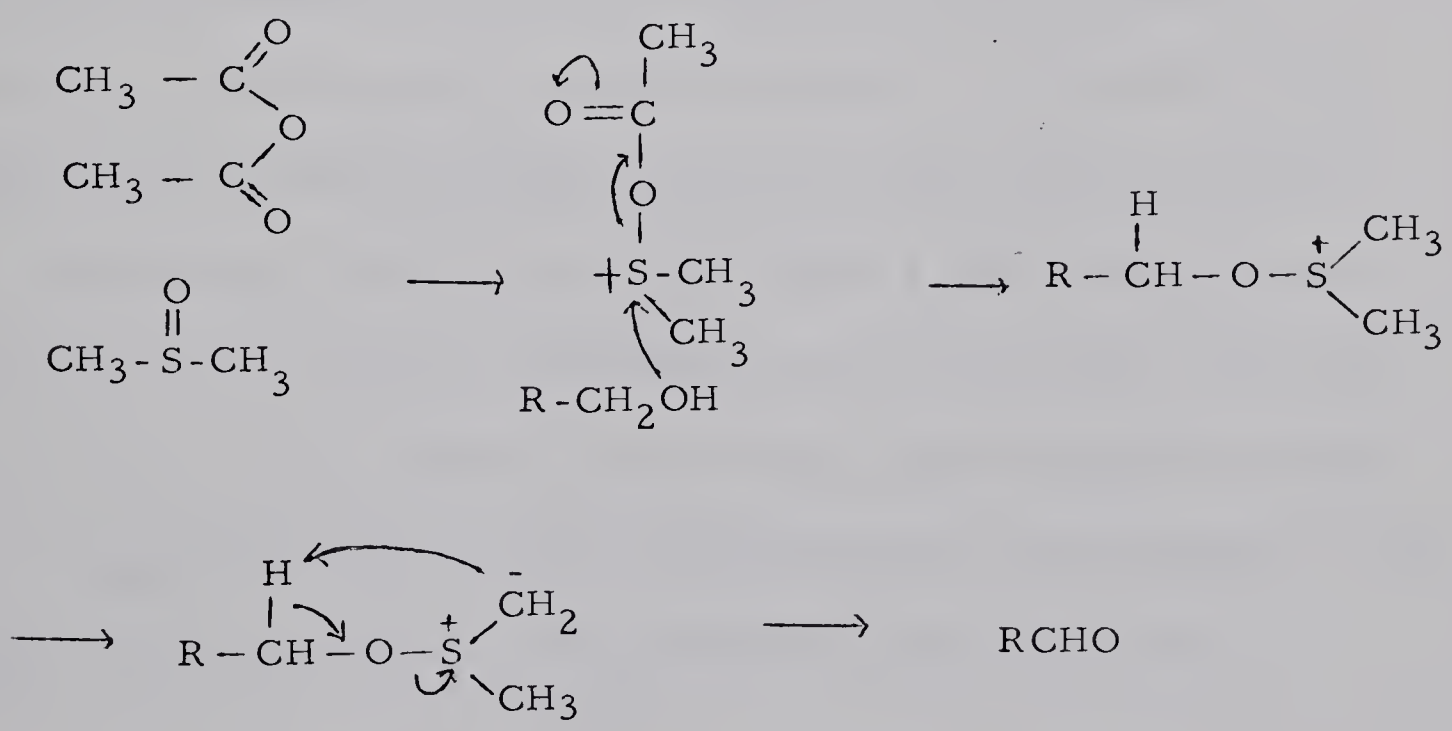
42 19a

3 - MECHANISM OF OXIDATION

The mechanism suggested for the DMSO, DCC-oxidation reaction[21] is shown in Scheme II while that of DMSO, acetic anhydride[22] in Scheme III.

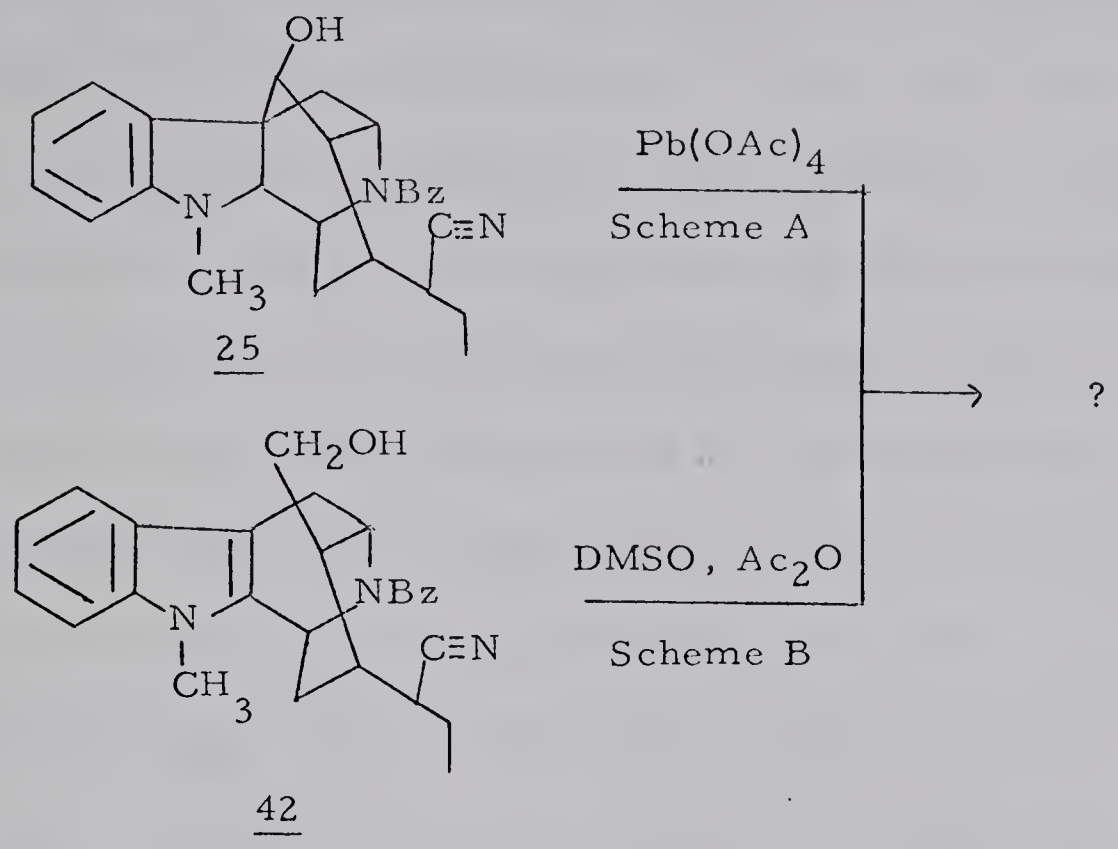


SCHEME II



SCHEME III

4 - INTERPRETATION OF RESULTS



Although we assumed previously that lead tetraacetate oxidation of 25 (Scheme A) resulted in demethylation at N_a, oxidation of 42 with DMSO and acetic anhydride afforded a compound almost identical in spectral data with the product obtained by Scheme A. It was difficult to rationalize that the DMSO treatment should also have effected demethylation. Furthermore, with compound 46 in which a carbomethoxy group was attached to N_b, oxidation with DMSO proceeded normally. But if 19a was the structure of the oxidation product of 42, why then was the sharp singlet normally attributed to N-CH_3 absent from the nmr spectrum? This and other related questions are discussed in the following section.

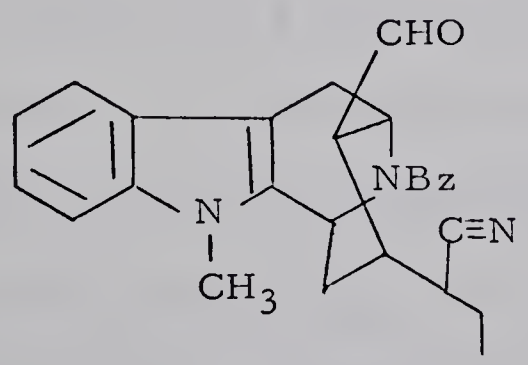
STUDY OF THE KEY INTERMEDIATE 19a

1 - STRUCTURE

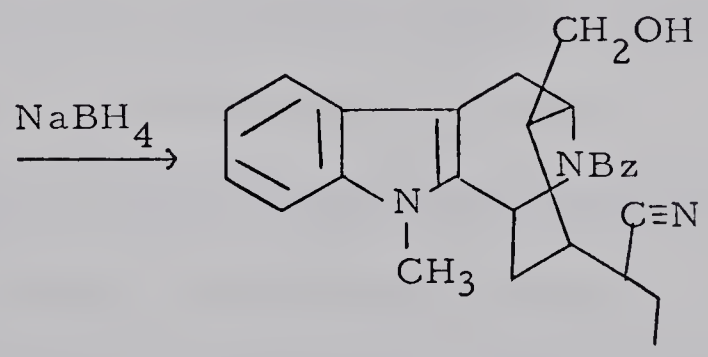
The final steps in both Schemes A and B afforded product whose

infrared and nmr spectra were similar but not superimposable. Since it was not easy to explain why demethylation should occur in Scheme B, the absence of defined N-C<u>H</u>$_3$ and C<u>H</u>O signals in the nmr spectrum was thought to be due to its temperature dependence. This was proven by taking an nmr spectrum (100 mc) of compound <u>19a</u> obtained by Scheme B at 80°. This showed the presence of N_a-C<u>H</u>$_3$ and C<u>H</u>O protons as sharp signals in contrast to the very broad peaks obtained at room temperature.

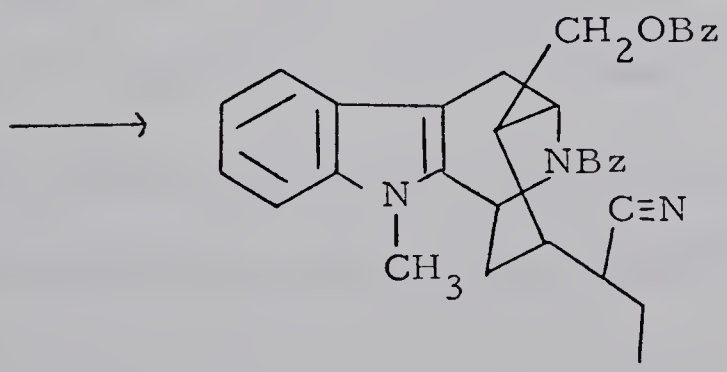
At this stage of the work, we did not know whether the products obtained from Schemes A and B were identical or not with respect to the stereochemistry at C_{16}. The material obtained from lead tetraacetate oxidation of <u>25</u> was reduced with sodium borohydride affording the alcohol (<u>42a</u>). Benzoylation of <u>42a</u> provided <u>41a</u> similar in spectral data with that of <u>41</u> (Scheme I, page 23).



<u>19b</u>



<u>42a</u>

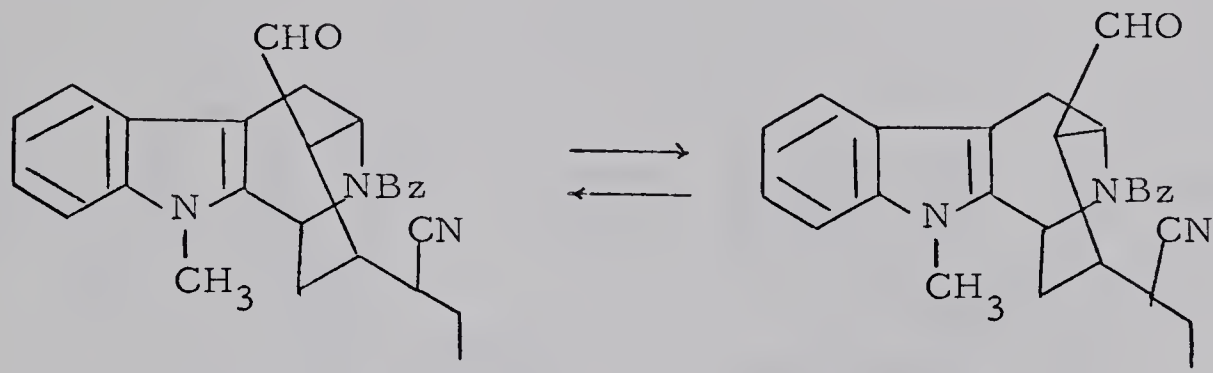


<u>41a</u>

In summary, both schemes afforded the desired key intermediate. However, there was a slight difference in their spectral data which could be due to different stereochemistry at C_{16}.

2 - STEREOCHEMISTRY OF 19a AND 19b

The stereochemistry at C_{16} of 19 became the subject of studies after its structure was confirmed. 19 can exist in two epimeric forms 19a and 19b, 19b being the more stable epimer. So far only the A-epimer was believed to have been isolated. It was finally discovered by C. E. Egli



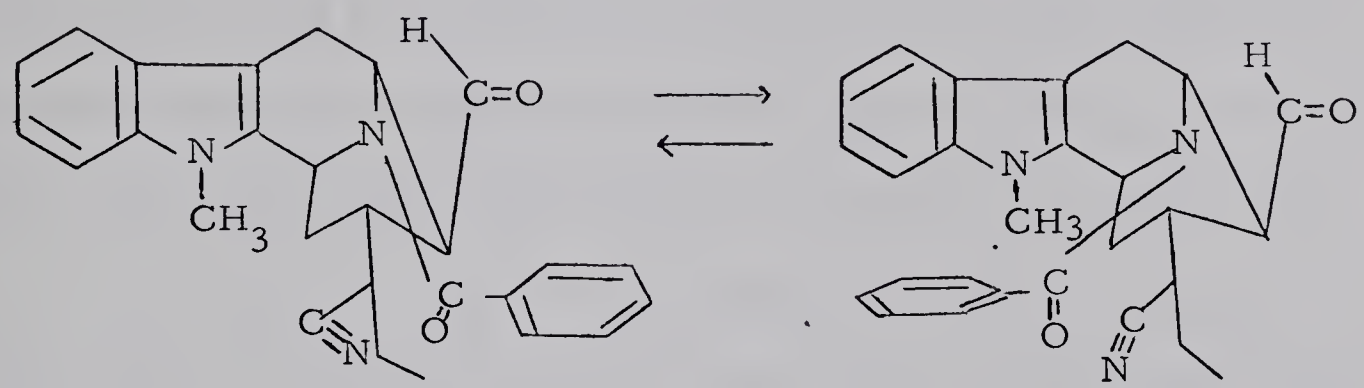
19a 19b

and S. K. Sarkar[23] by a series of reactions that neutral alumina caused epimerization of the aldehyde group at C_{16}. Oxidation of 25 by lead tetraacetate, followed by neutral work-up and chromatography on silicic acid afforded crystalline 19a. S. K. Sarkar also found that the latter compound when treated with alumina gave an equilibrium mixture of 19a (30%) and 19b (70%). 19b was obtained in nearly pure form, but was not induced to crystallize. Therefore compound 19 mentioned earlier (page 18) in which the stereochemistry at C_{16} was not specified should be 19b. Compounds 42a and 41a (see page 29) were epimers of 42 and

and 41 respectively (see page 23).

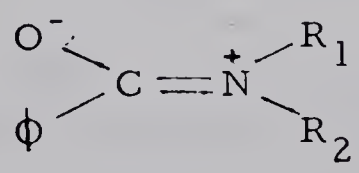
3 - NMR STUDY OF 19a

The 100 mc nmr spectrum of 19a at 23.5° consisted of two aldehyde signals separated by 25 cps and two N-CH_3 signals separated by 29 cps. The behavior of the aldehyde group in the nmr spectrum is discussed in detail below (the N-CH_3 behaved similarly). The chemical shift between the aldehyde signals was due to their different environments as shown in structures A and B. One would expect free rotation about a single



A B

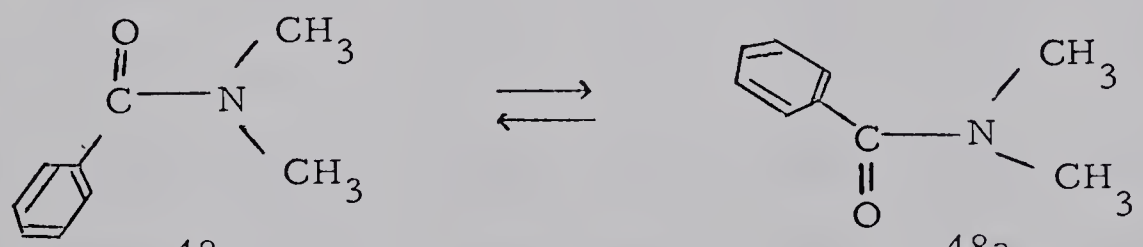
bond but the C-N bond in amides could assume double bond character owing to resonance form of the type



and the rate of this rotation is slow compared to rotation around a single bond. The basis for a quantitative study[24] of the rates of rotation has been developed by Gutowsky et al.[25] (see appendix). The nmr signals

at 23.5° for aldehyde were due to the two interchanging species A and B when the populations were equal. However at 60° the internal rotation occurred at a sufficiently rapid rate for the effective chemical shifts to be averaged. Thus, an examination of a spectrum at different temperatures (see figure 1) provided values of interconversion rate k (see Table I) from which the activation energy E_a was obtained and found to be 10.5 kcal/mole. The activation parameters $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$ and $\Delta F^{\ddagger}$ as defined by the Eyring rate equation were 9.9 kcal/mole, -20.1 cal/mole and 15.98 kcal/mole respectively at 30°.

That the benzoyl group attached to N_b in structure 19a caused a temperature dependence behavior in the nmr spectra is due to the diamagnetic anisotropic effect of the benzene ring in the interconverting species. In structure A (page 31) the aldehyde proton held directly above the ring was shielded and the N_a-CH_3 situated on the plane of the ring was deshielded. The reverse was true in structure B. This behavior was also exhibited in the nmr spectra of N,N-dimethyl benzamide 48 whose



48 ⟷ 48a

data are shown in Table II (page 34). The activation energy E_a calculated for 48 was 11.03 kcal/mole. The activation parameters $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, $\Delta F^{\ddagger}$ as defined by the Eyring rate equation were 10.43 kcal/mole, -16.95 cal/mole and 15.62 kcal/mole respectively at 28.5°.

In accord with this view, anhydro-N_b-acetylajmalal oxime-A (51) did not show temperature dependence in the nmr spectrum (figure 2).

TABLE I

OBSERVED FREQUENCIES AND INTENSITY RATIOS AND CALCULATED PARAMETERS FROM THE NMR SPECTRUM OF 19a AT SELECTED TEMPERATURES

δ = 25 cps E_a = 10.5 kcal/mole

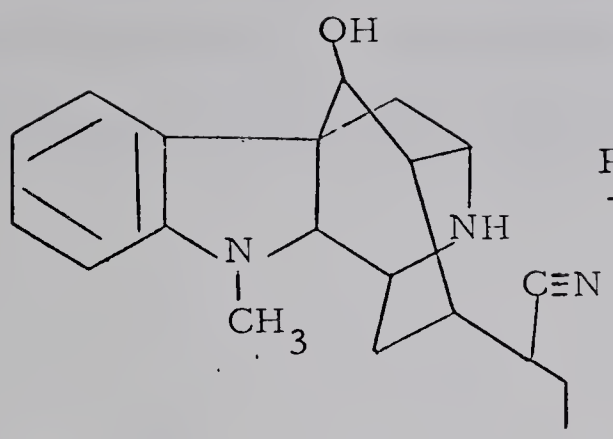
Corr. Temp. °C	Δ cps	K	ln k	α calc.	α ob.	$\Delta H^{\ddagger}$ kcal/mole	$\Delta S^{\ddagger}$ cal/mole	$\Delta F^{\ddagger}$ kcal/mole
28.9	24	15.51	2.759	0.15	0.16	9.9	-19.55	15.79
30.0	24	15.51	2.759	0.15	0.13	9.9	-20.1	15.98
31.0	23	21.73	3.07	0.28	0.20	9.89	-19.55	15.84
32.2	23	21.73	3.07	0.28	0.26	9.89	-19.69	15.90
33.2	22	26.35	3.264	0.40	0.37	9.89	-19.39	15.83
34.3	20.5	31.75	3.45	0.54	0.41	9.89	-19.15	15.78
35.4	20	33.29	3.49	0.59	0.47	9.88	-19.20	15.82
36.4	18.5	37.05	3.61	0.70	0.63	9.88	-19.05	15.77
37.5	18	38.50	3.66	0.73	0.62	9.88	-19.05	15.79
38.6	15.5	43.33	3.77	0.85	0.71	9.88	-19.0	15.81
39.6	14.5	45.22	3.80	0.88	0.72	9.88	-19.03	15.83
40.8	12.5	48.04	3.86	0.94	0.73	9.88	-19.04	15.85

TABLE II

OBSERVED FREQUENCIES AND INTENSITY RATIOS AND CALCULATED PARAMETERS FROM THE NMR SPECTRUM OF 48 AT SELECTED TEMPERATURES

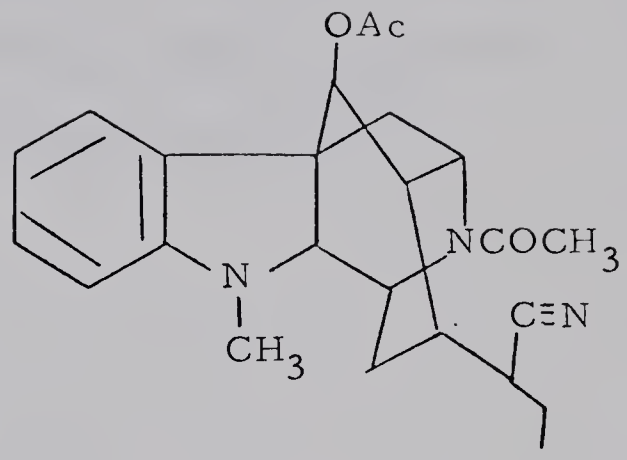
δ = 16.9 cps E_a = 11.03 kcal/mole

Corr. Temp. °C	Δ cps	K	ln k	α calc.	α ob.	$\Delta H^{\ddagger}$ kcal/mole	$\Delta S^{\ddagger}$ cal/mole	$\Delta F^{\ddagger}$ kcal/mole
0	16.7	5.652	1.70	0.04	0.0	10.49	-16.3	14.89
20	15.0	16.95	2.80	0.38	0.36	10.45	-16.85	15.38
25	12.6	24.8	3.197	0.69	0.68	10.44	-16.7	15.41
27.5	9.5	30.77	3.427	0.90	0.96	10.43	-16.64	15.44
28.5	7.2	33.9	3.519	0.96	1.0	10.43	-16.95	15.41
33.5	0.0	37.36	3.61	1.0	1.0	10.42	-16.65	15.62



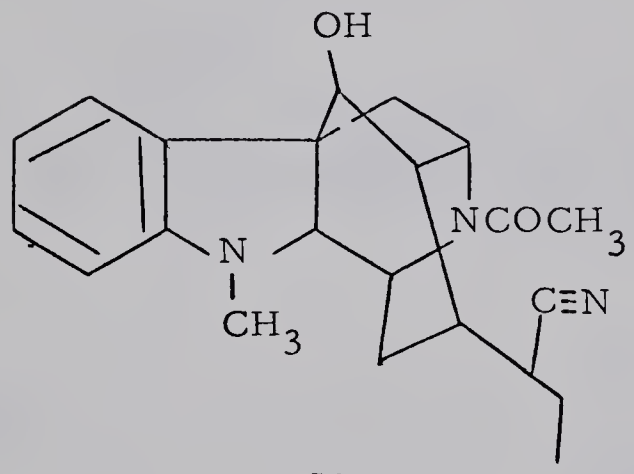
24

Py , Ac_2O →



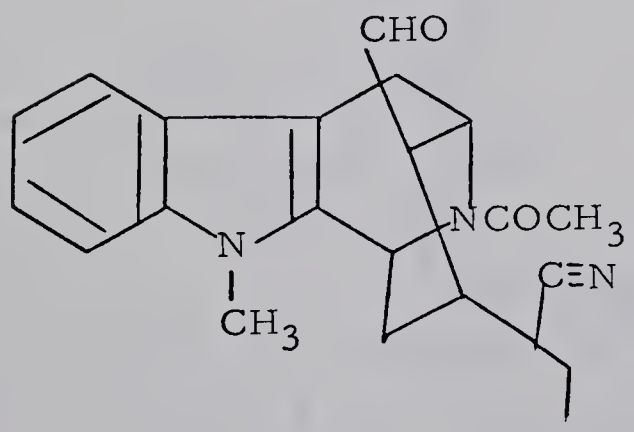
49

NaOMe →



50

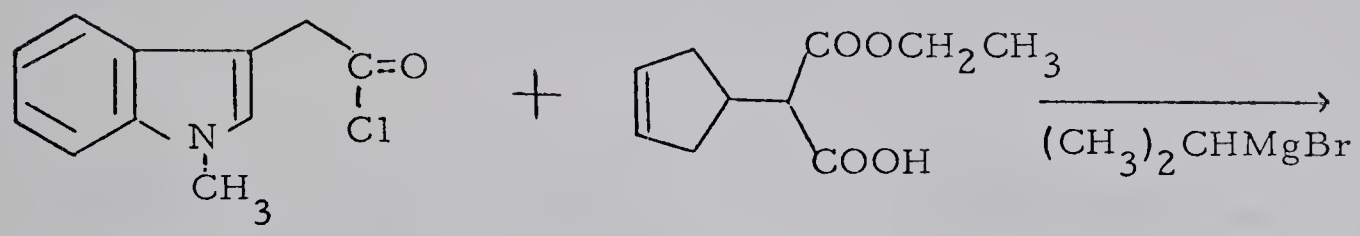
Pb(OAc)4 →



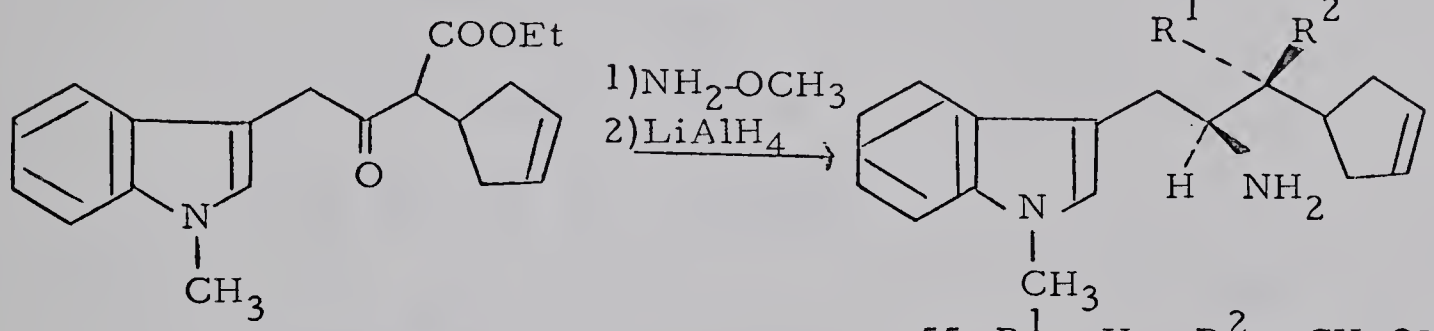
51

TOTAL SYNTHESIS OF AJMALINE

The total synthesis of ajmaline accomplished by S. Masamune et al.[26] is outlined in Scheme IV. The synthetic compounds 58, 58a, 59, 60, and 60a were identical with 41, 41a, 42, 42a, 19a and 19b, respectively.



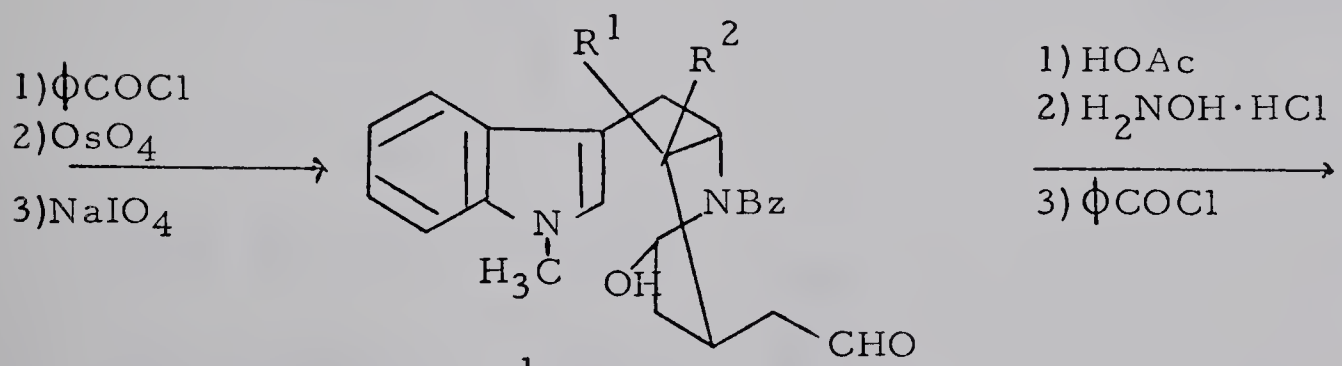
52 53



54

55 R^1 = H R^2 = CH_2OH

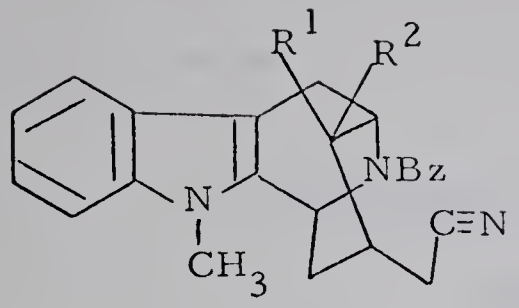
55a R^1 = CH_2OH R^2 = H



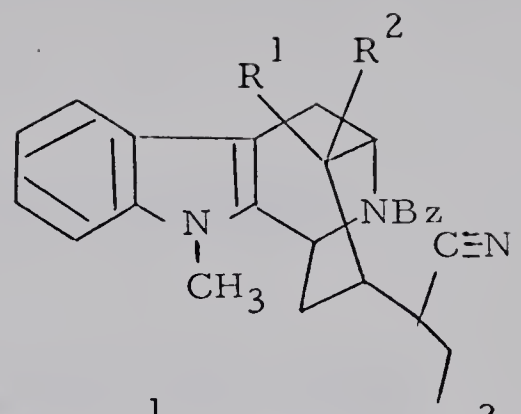
56 R^1 = CH_2OBz R^2 = H

56a R^1 = H R^2 = CH_2OBz

SCHEME IV



1) ϕ_3-CNa
2) CH_3CH_2Br



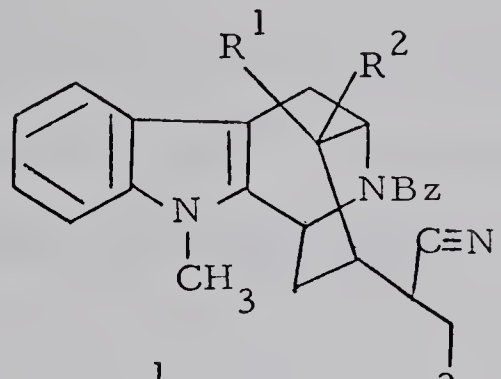
57 $R^1 = CH_2OBz$ $R^2 = H$

57a $R^1 = H$ $R^2 = CH_2$-OBz

58 $R^1 = CH_2OBz$ $R^2 = H$

58a $R^1 = H$ $R^2 = CH_2OBz$

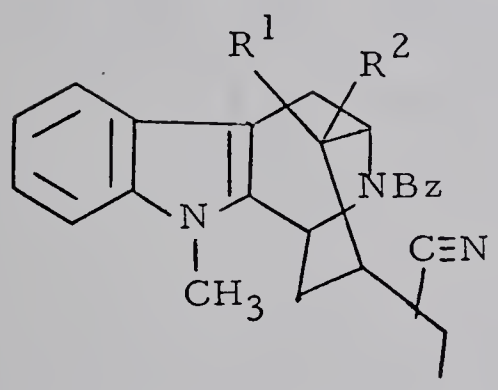
NaOMe →



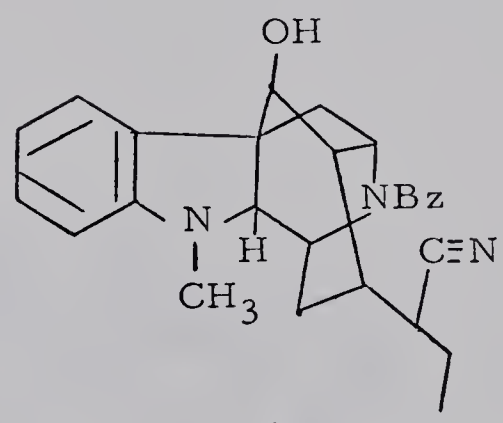
DMSO, Ac_2O →

59 $R^1 = CH_2OH$ $R^2 = H$

59a $R^1 = H$ $R^2 = CH_2OH$



1) Ac_2O-HOAc
2) hydrogenation

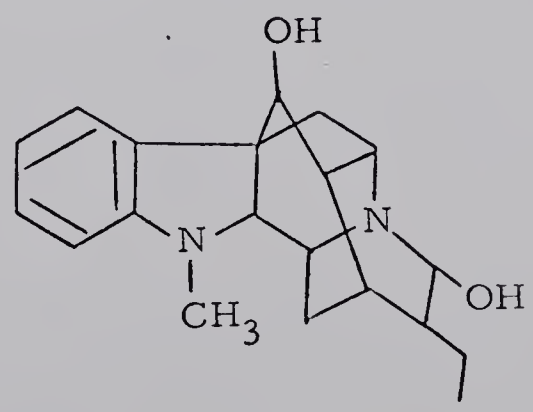


60 $R^1 = CHO$ $R^2 = H$

61a $R^1 = H$ $R^2 = CHO$

61

1) $LiAl(OEt_3)H$
2) Hydrogenolysis
3) $LiAlH_4$



1

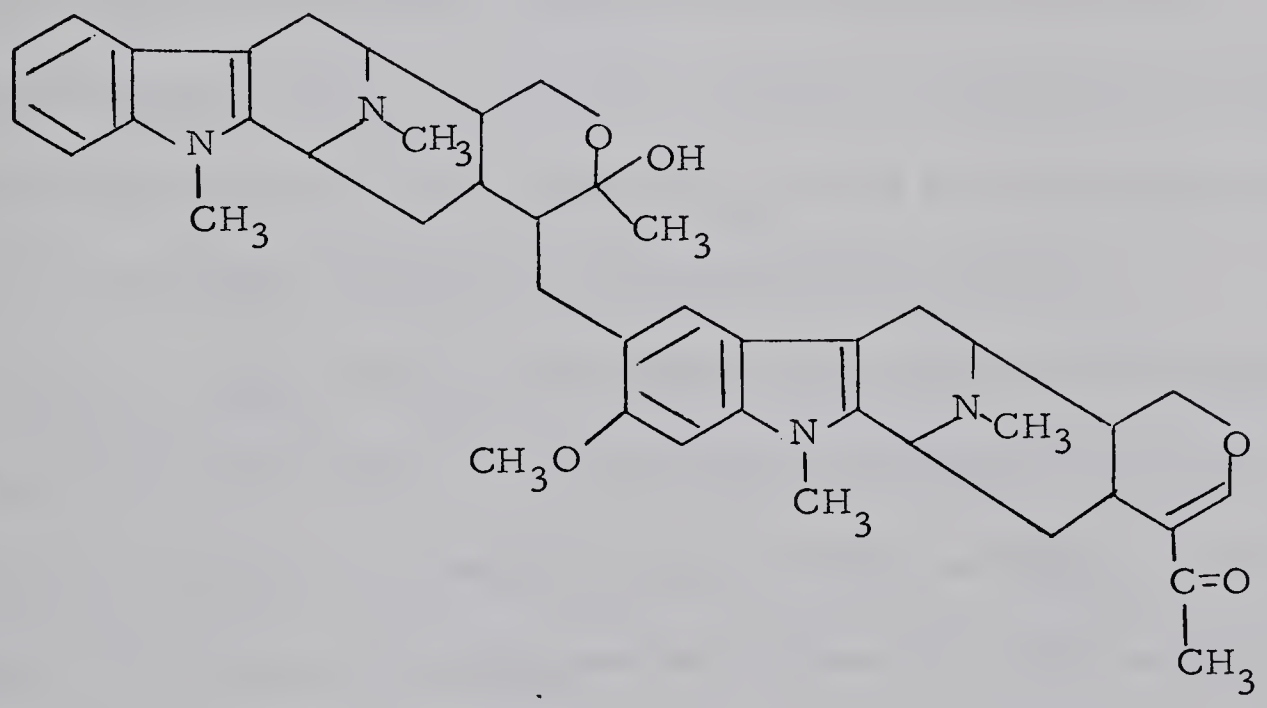
SCHEME IV CONT'D.

Compound 19a served as a relay compound and was converted to ajmaline in several steps.

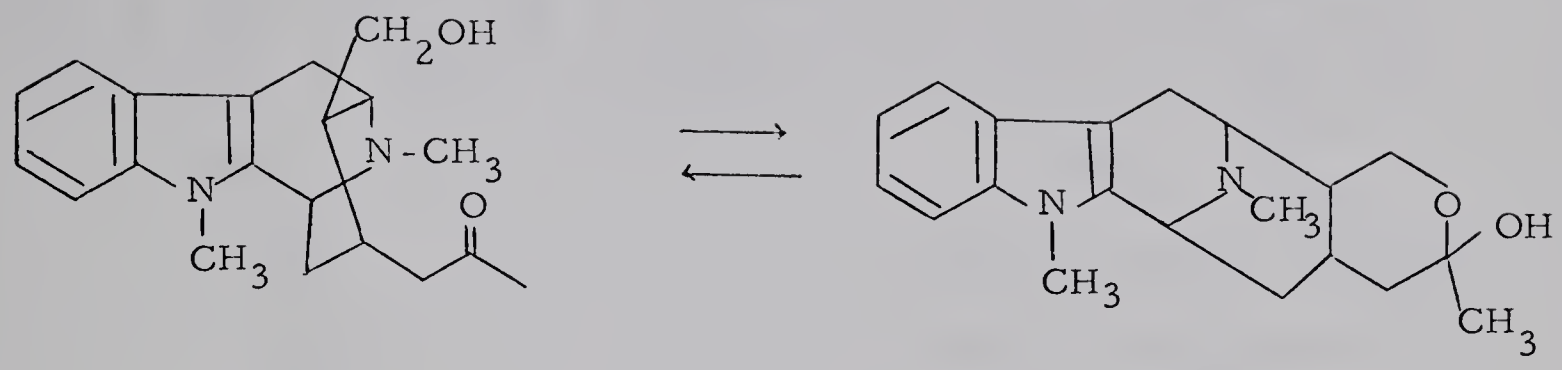
B - SYNTHESIS OF DESMETHYLENEMACROLINE

GENERAL

Macralstonin (62) is a dimeric alkaloid isolated from Alstonia macrophylla, family Apocynacae, by Sharp in 1934.[27] Upon acid hydrolysis of 62 three components were obtained, one of which was desmethylenemacroline (63) whose structure and stereochemistry were proposed by Schmid et al.[28] They also reported a 2:1 equilibrium between 63 and 63a in favor of the open form.



62

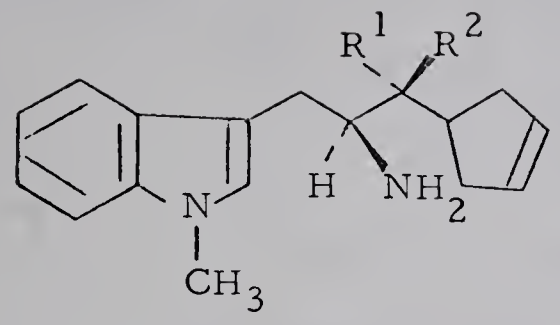


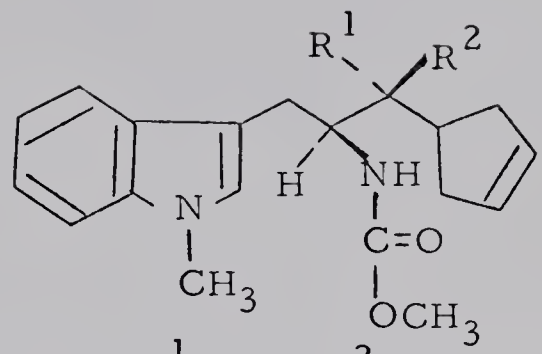
63 ⇌ 63a

SYNTHESIS

The scheme for synthesis of desmethylenemacroline 63 was patterned after the procedure utilized in the ajmaline synthesis. A modified scheme is shown in Scheme V, where a carbomethoxy group was used in place of a benzoyl group at N_b, since a carbomethoxy group could be conveniently reduced to the desired N-CH_3 group.

Reaction of (55) and (55a) with methyl chloroformate afforded the corresponding carbomethoxy compounds (64) and (64a) respectively. The latter pair of epimers on acetylation provided (65) and (65a) which on oxidation with osmium tetroxide gave amorphous diols (66) and (66a). On one occasion 66a was obtained as a crystalline solid, however, this result could not be reproduced. Since the α and β sides of the cyclopentane ring offered no difference in steric hindrance, attack by reagent at the double bond was possible from both sides. The formation of crystalline 66a suggested that the reaction was stereospecific and was interpreted as accidental. Oxidation of the diols 66 and 66a with





55

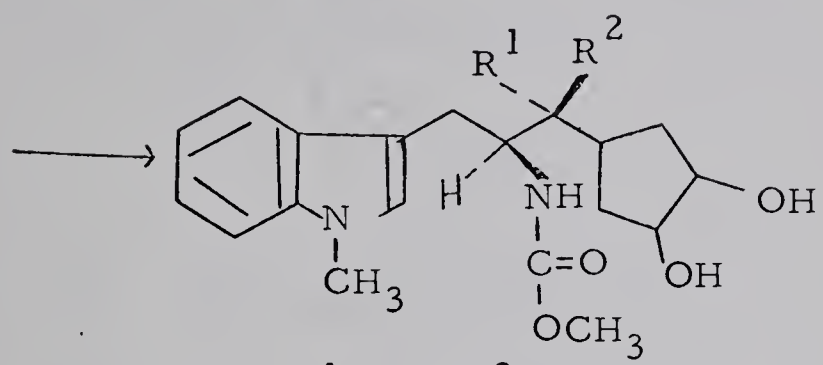
55a

64 $R^1 = H$ $R^2 = CH_2OH$

64a $R^1 = CH_2OH$ $R^2 = H$

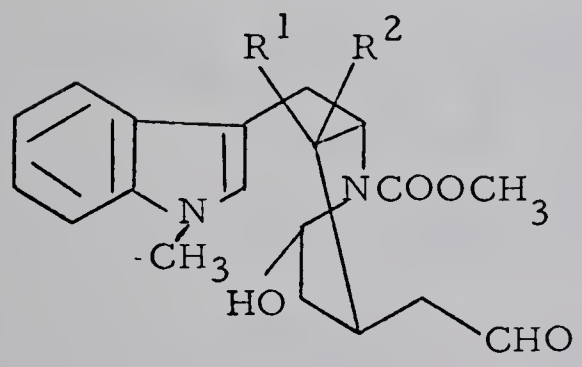
65 $R^1 = H$ $R^2 = CH_2OAc$

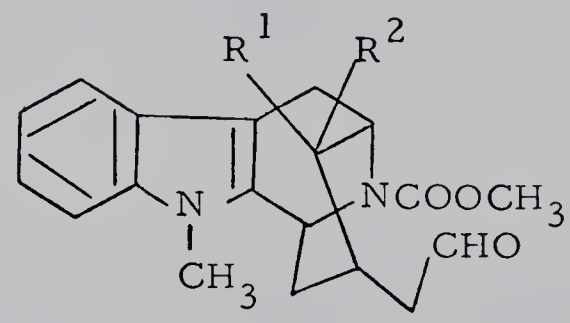
65a $R^1 = CH_2OAc$ $R^2 = H$



66 $R^1 = H$ $R^2 = CH_2OAc$

66a $R^1 = CH_2OAc$ $R^2 = H$





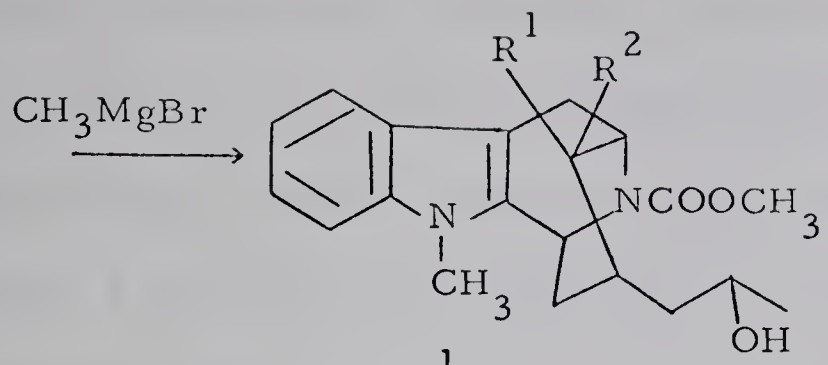
67 $R^1 = CH_2OAc$ $R^2 = H$

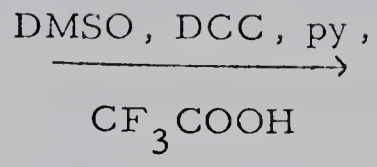
67a $R^1 = H$ $R^2 = CH_2OAc$

68 $R^1 = CH_2OAc$ $R^2 = H$

68a $R^1 = H$ $R^2 = CH_2OAc$

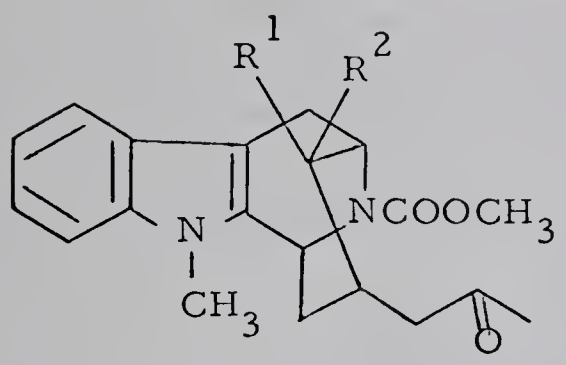
SCHEME V

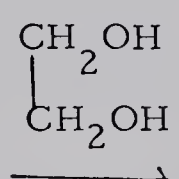


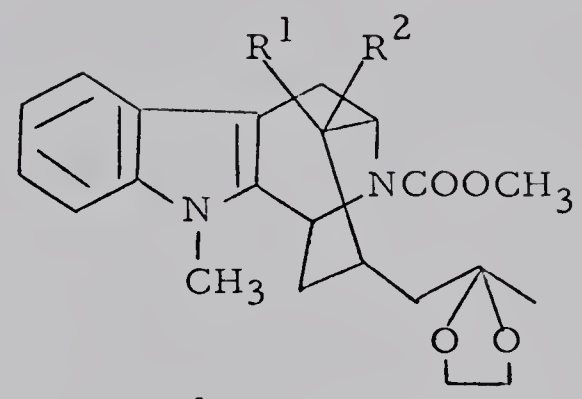


69 $R^1 = CH_2OAc$ $R^2 = H$

69a $R^1 = H$ $R^2 = CH_2OAc$





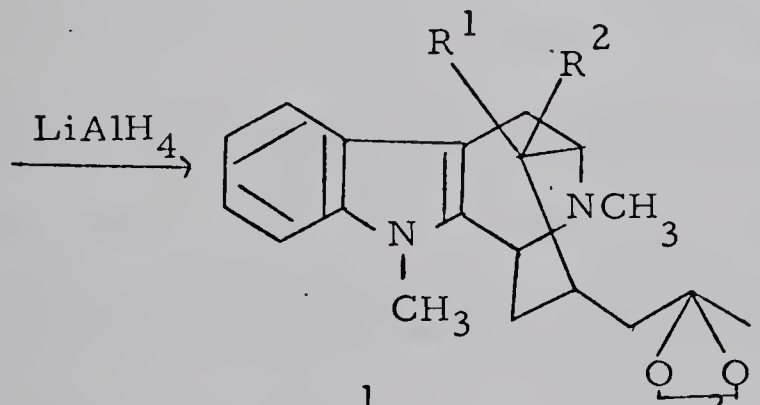


70 $R^1 = CH_2OAc$ $R^2 = H$

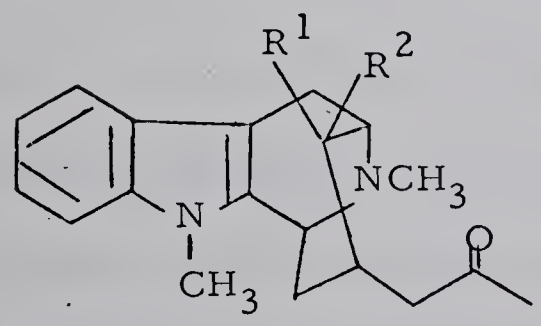
70a $R^1 = H$ $R^2 = CH_2OAc$

71 $R^1 = CH_2OAc$ $R^2 = H$

71a $R^1 = H$ $R^2 = CH_2OAc$



72 $R^1 = CH_2OH$ $R^2 = H$ 72a $R^1 = H$ $R^2 = CH_2OH$



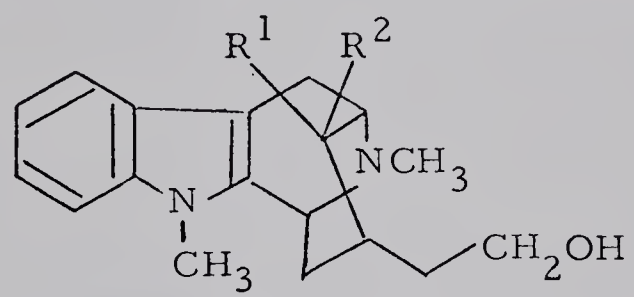
73 $R^1 = CH_2OH$ $R^2 = H$

73a $R^1 = H$ $R^2 = CH_2OH$

SCHEME V CONT'D

sodium metaperiodate afforded aldehydes (67) and (67a) respectively. Cyclization of the latter compounds afforded the tetracyclic compounds 68 and 68a. The nmr spectrum of 68a showed resonance at τ 0.5 (singlet, C<u>H</u>O), 4.5 (triplet, -C=C-C<u>H</u>-CH_2-), 5.4 (-CH_2-C<u>H</u>-N_b-CH_3), 5.9 (doublet, -C<u>H_2</u>-OAc), 6.32 and 6.42 (-N-C<u>H_3</u> and -O-C<u>H_3</u>) and 7.95 (singlet, C<u>H_3</u>CO-) while that of 68 is reproduced in figure 3 showing only a slight difference in chemical shifts of certain protons.

Structures 68 and 68a were further characterized by exhaustive reduction to the corresponding alcohols (74) and (74a) respectively. Both



74 $R^1 = CH_2OH$ $R^2 = H$

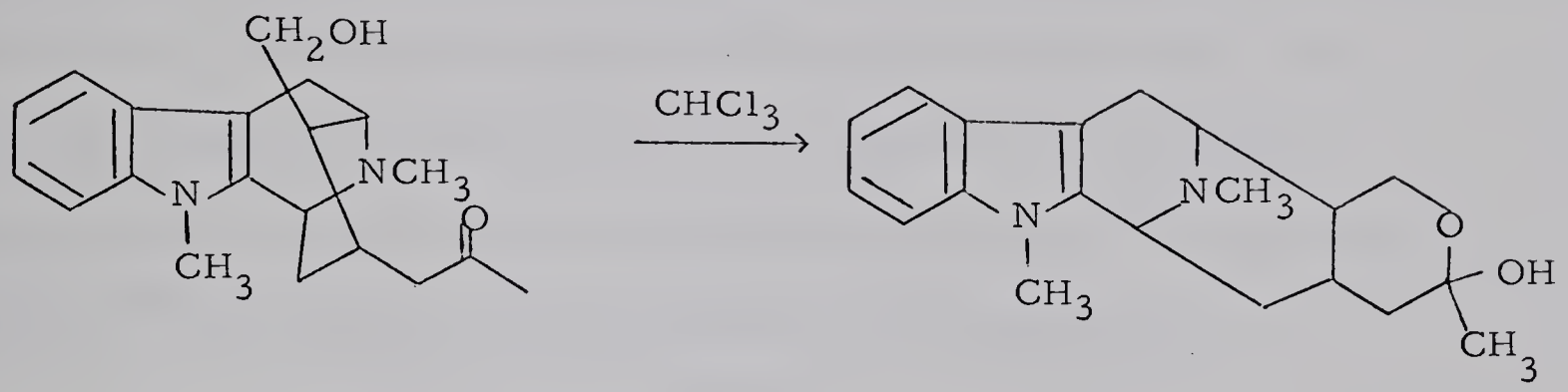
74a $R^1 = H$ $R^2 = CH_2OH$

compounds 74 and 74a had identical mass spectra and displayed prominent peaks at m/e 314 (M^+), 227, 197, 182, 170, 157 and 144 which are characteristic of ajmaline type compounds.

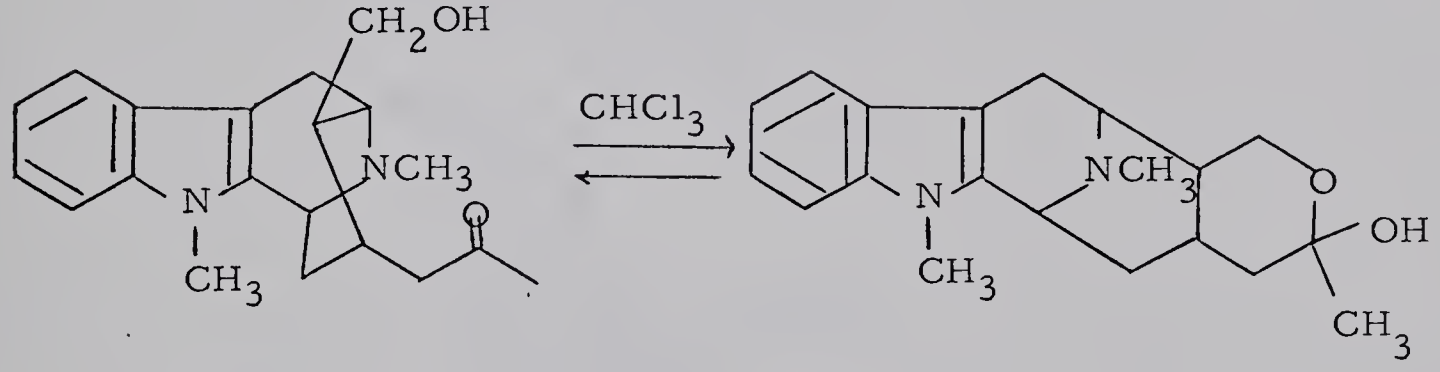
Reaction of aldehydes 68 and 68a with methyl magnesium bromide provided alcohols (69) and (69a) respectively, the latter epimers on oxidation with DMSO, DCC and pyridinium trifluoroacetate afforded the corresponding ketones (70) and (70a). The ketals (71) and (71a) were reduced with lithium aluminum hydride affording (72) and (72a) which on hydrolysis with p-toluenesulfonic acid provided the desired compounds (73) and (73a) respectively.[29]

COMMENTS

Compound 73 existed in its hemiacetal form (75) in chloroform solution as evidenced by the absence of carbonyl absorption in the infrared spectrum. On the other hand, a 6:4 equilibrium of 75a and 73a in favor of hemiacetal 75a was observed. These results are not



73 75



73a 75a

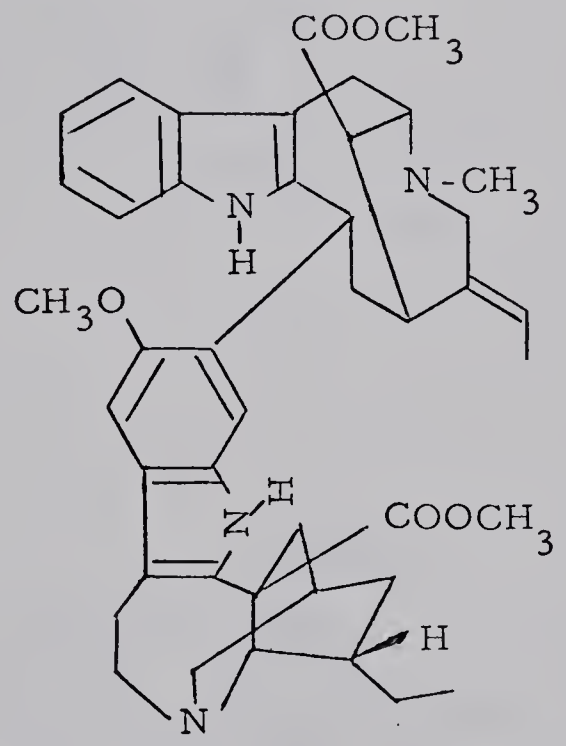
in agreement with those of Schmid. Although compounds 63, 73 and 73a showed identical mass spectra, their infrared spectra differed significantly. These discrepancies are being investigated by S. Masamune et al. Recently, a private communication between S. Masamune and Schmid revealed that desmethylenemacroline obtained from the natural product was not pure and this caused the observed discrepancies in spectral data between the natural and synthetic materials.

PART II - AN APPROACH TO THE SYNTHESIS OF 2-ACYLINDOLE TYPE ALKALOIDS

A - DEGRADATION OF AJMALINE TO 2-ACYLINDOLE TYPE ALKALOIDS

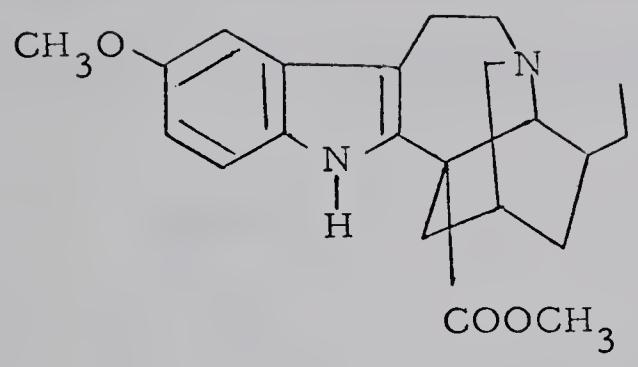
GENERAL

Recent investigations of the genus Voacanga, revealed the presence of four groups of bases. These are sarpagine, 2-acylindole seco-sarpagine derivatives, carbomethoxymethyleneindoline and dimeric types. Of the dimeric alkaloids, voacamine (76) was isolated from Voacanga africana and its structure was elucidated by Buchi et al.[30] The partial synthesis[30] of voacamine has been achieved by condensation of



76

voacangine (77) with vobasinol (78). Voacangine 77 is the prototype of a group of alkaloids containing an iso-quinuclidine ring. Vobasinol 78 was obtained by reduction of the natural product vobasine (79) which is representative of alkaloids containing the characteristic 2-acylindole moeity. Biogenetically, the 2-acylindole type alkaloids my be derived



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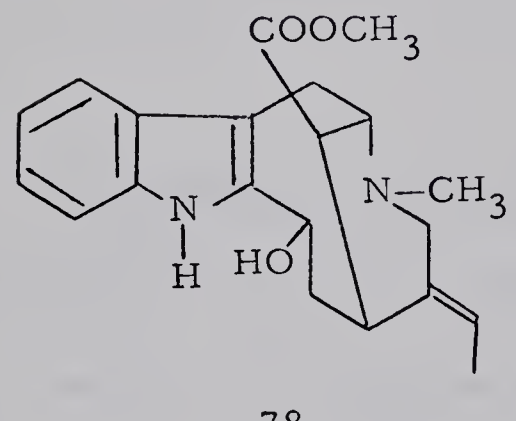
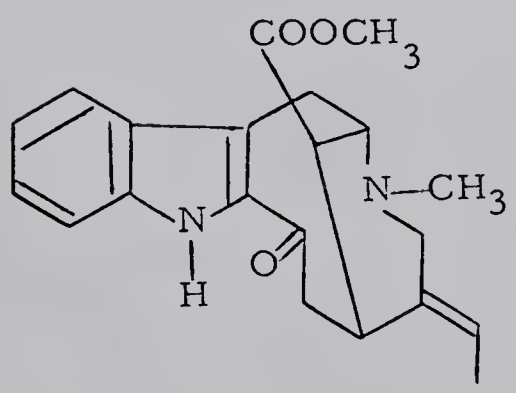
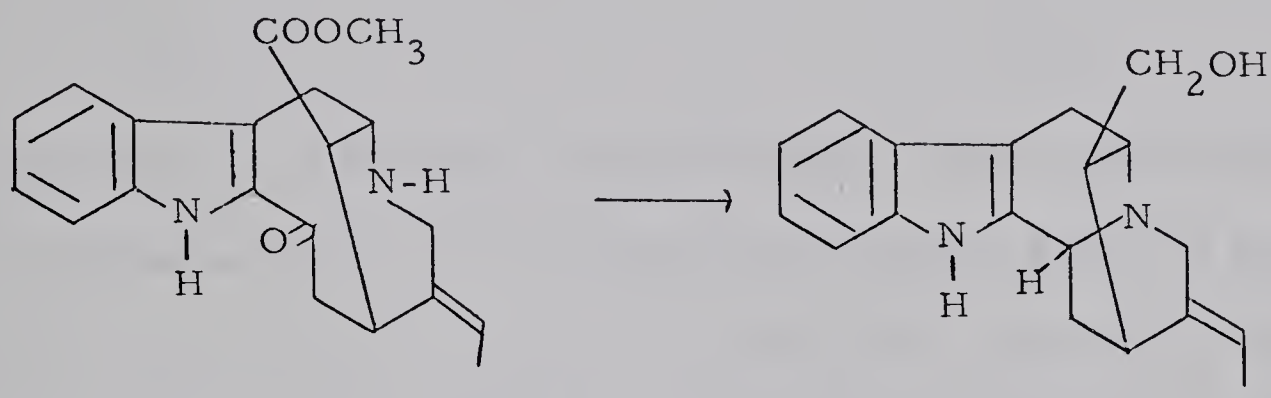


78



79

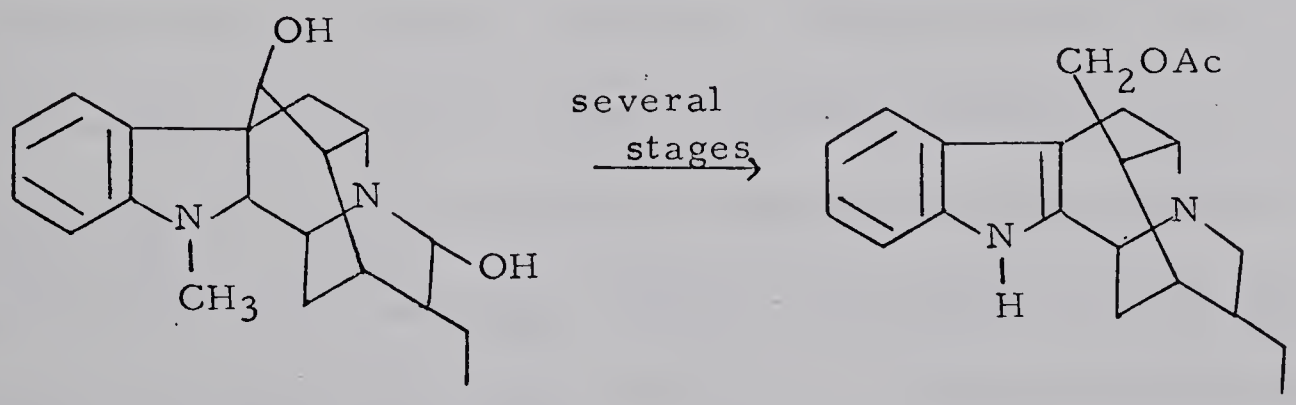
from sarpagine-type compounds or vice versa. The last suggestion was confirmed by converting perivine (80) to normacusine-B (81) identical in all respect with the natural product.[30] Our task was to achieve a synthesis of vobasine-type compounds from ajmaline.



80 81

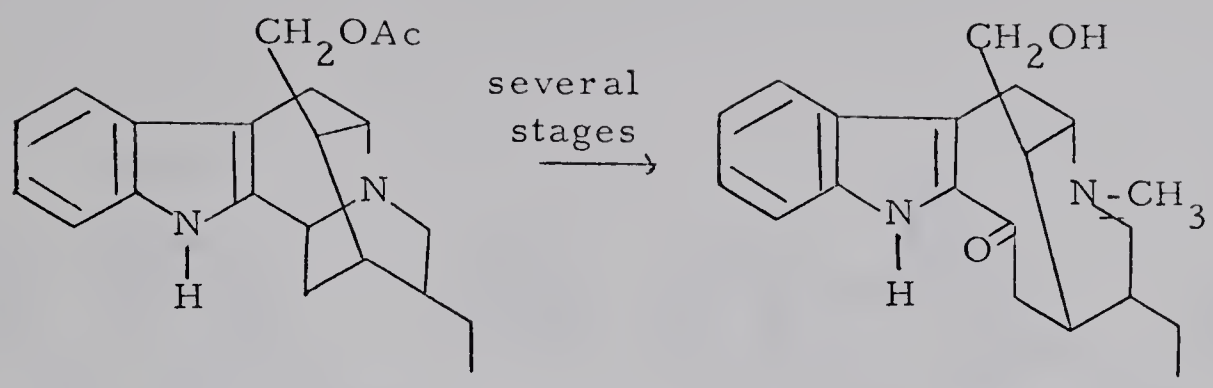
ATTEMPTED SYNTHESIS

The conversion of ajmaline 1 to a 2-acylindole type compound was divided into two parts, namely; (a) degradation of ajmaline to a sarpagine-type compound,



1 87

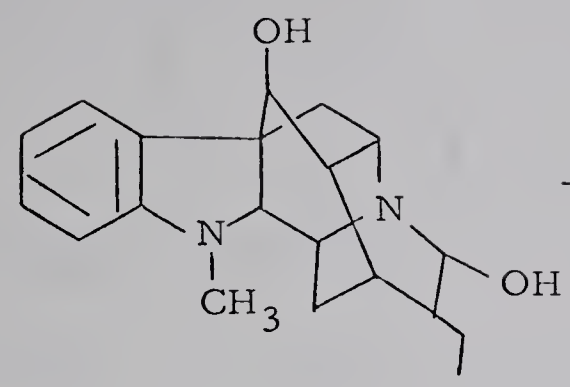
(b) C-D ring cleavage of the sarpagine-type compound.



87 101

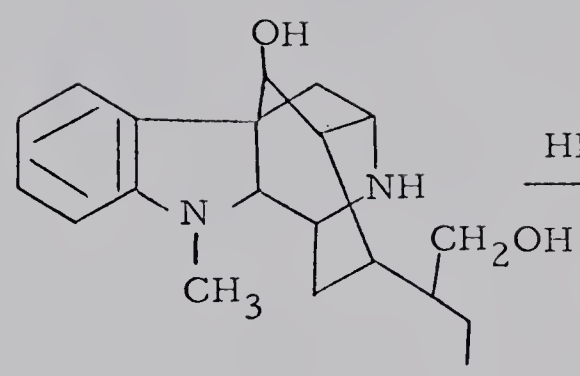
DEGRADATION OF AJMALINE TO SARPAGINE-TYPE COMPOUND

Degradation of ajmaline 1 to deoxydihydrosarpagine (86a) has been achieved by Taylor et al.[31] as outlined in Scheme VI. Ajmaline 1 was first converted to deoxyajmaline 14 by two known steps. It was mentioned earlier that deoxyajmaline was readily oxidized by lead tetraacetate to an indole aldehyde. However, in the presence of excess lead tetraacetate, deoxyajmaline-O-acetate (83) was demethylated to afford the indolenine (84). Hydrolysis of 84 with sodium hydroxide provided N_a-demethyldeoxy-ajmalal-B (85a) which on reduction with sodium borohydride yielded deoxydihydrosarpagine (86a). Acetylation of 86a gave the O-acetyl derivative (87a). In our case, 85a was obtained by hydrolysis of indolenine 84 with sodium methoxide. Reduction of 85a with lithium aluminum hydride provided 86a. However, our interest was to obtain N_a-demethyldeoxyajmalal-A (86). This was accomplished by reduction of indolenine 84 with lithium aluminum hydride to yield 86. Acetylation of 86 gave O-acetyl derivative (87) in 50% yield and diacetyl derivative (88).



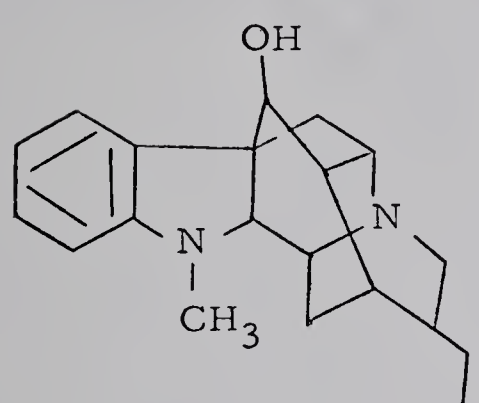
1

KBH_4



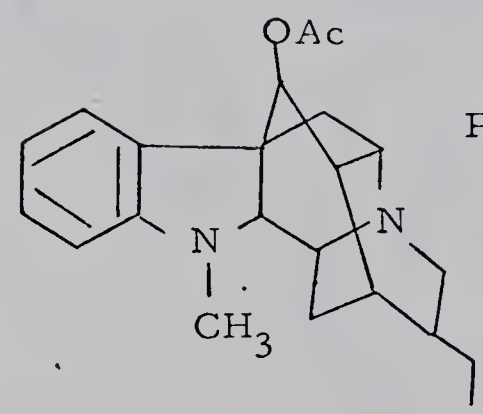
82

HBr



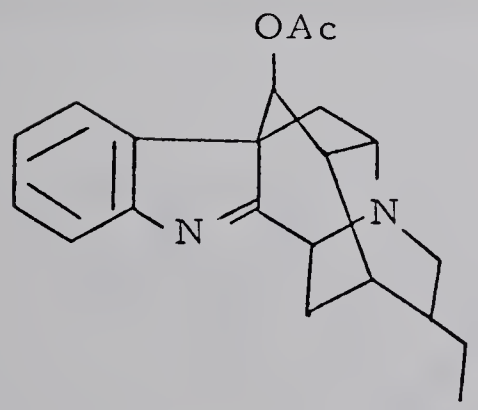
14

Ac_2O, py



83

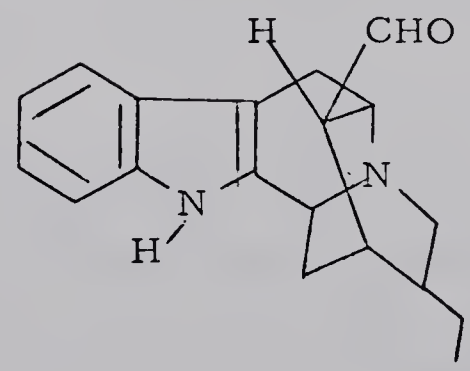
$Pb(OAc)_4$



84

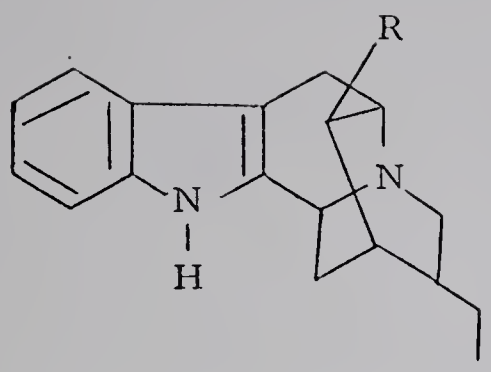
2N NaOH

or NaOMe



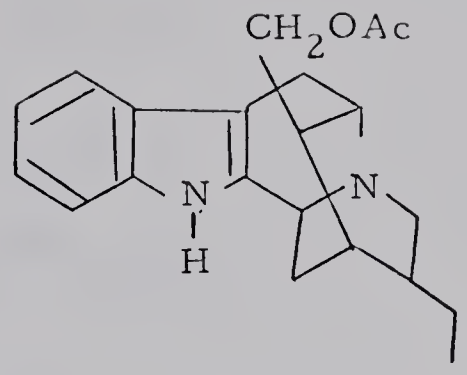
85a

SCHEME VI



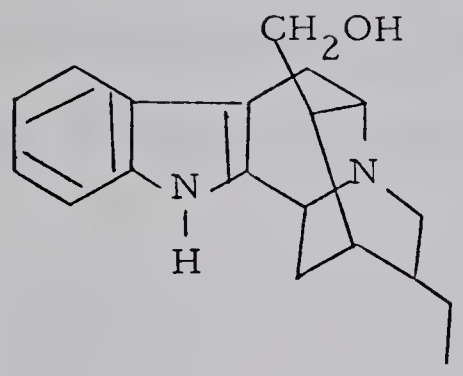
86a R = CH_2OH

87a R = CH_2OAc

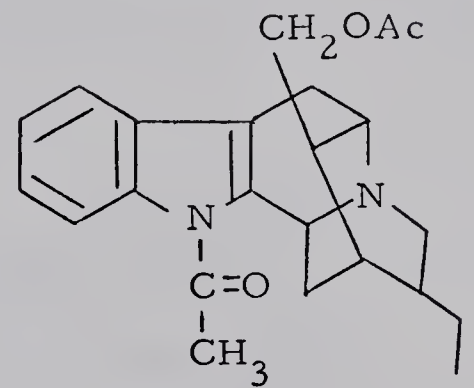


87

84 $\xrightarrow{LiAlH_4}$



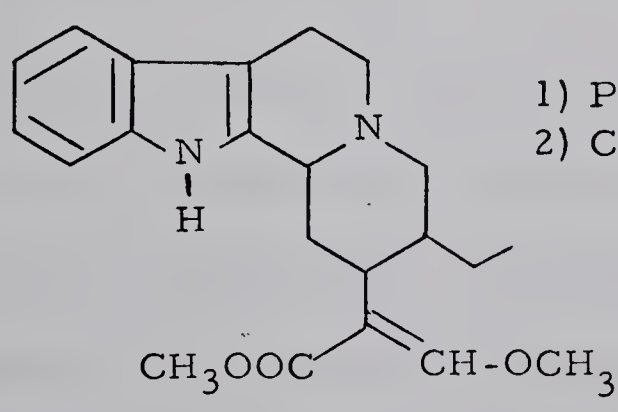
86



88

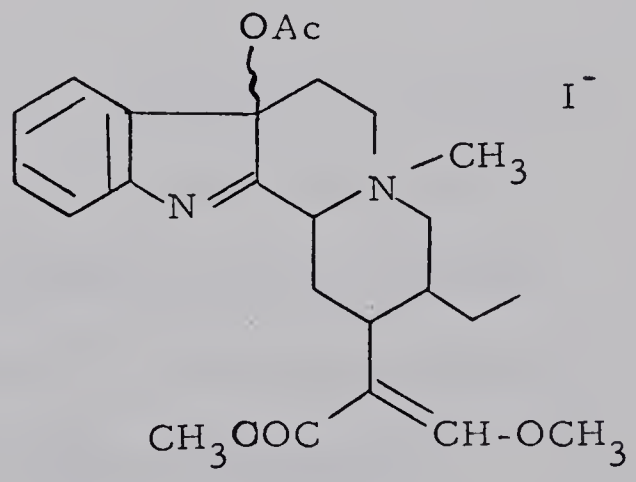
C-D RING CLEAVAGE OF THE SARPAGINE-TYPE COMPOUND

C-D ring cleavage has been reported by Dolby and Sakai[32] for dihydrocorynantheine (89) as outlined in Scheme VII. This scheme was



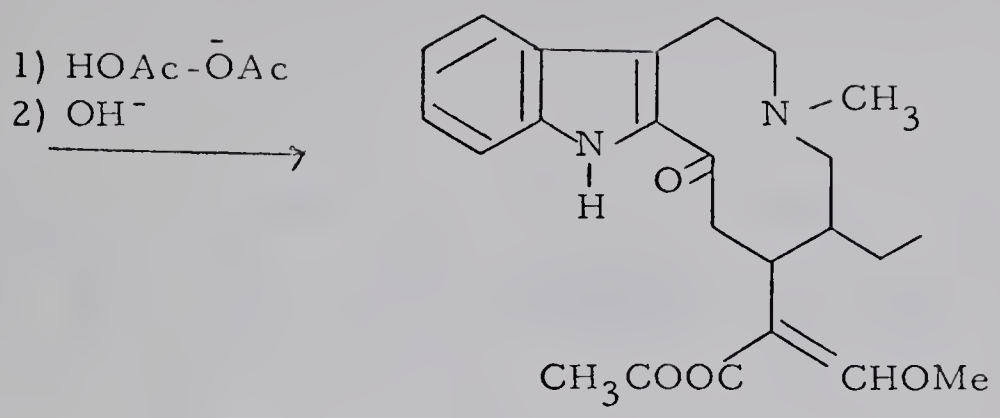
89

1) $Pb(OAc)_4$
2) CH_3I $\longrightarrow$



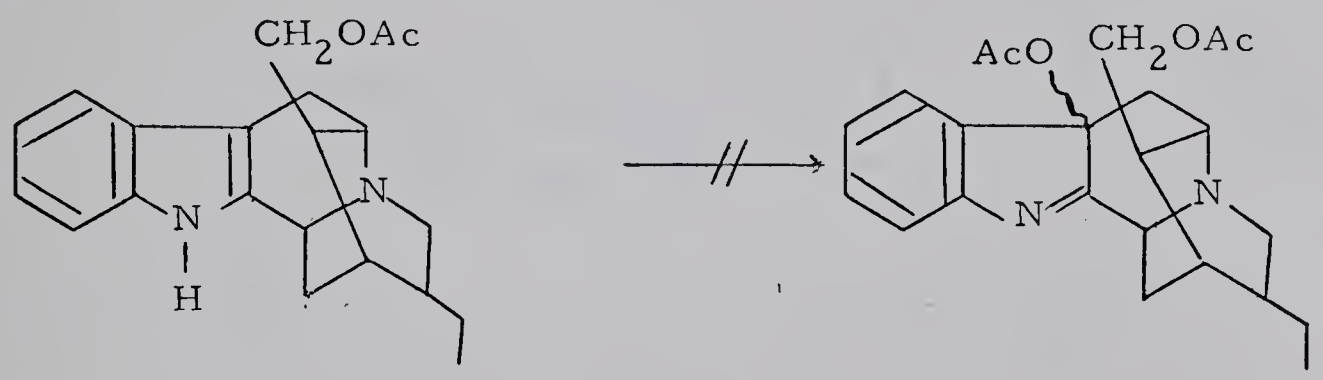
90

SCHEME VII



91

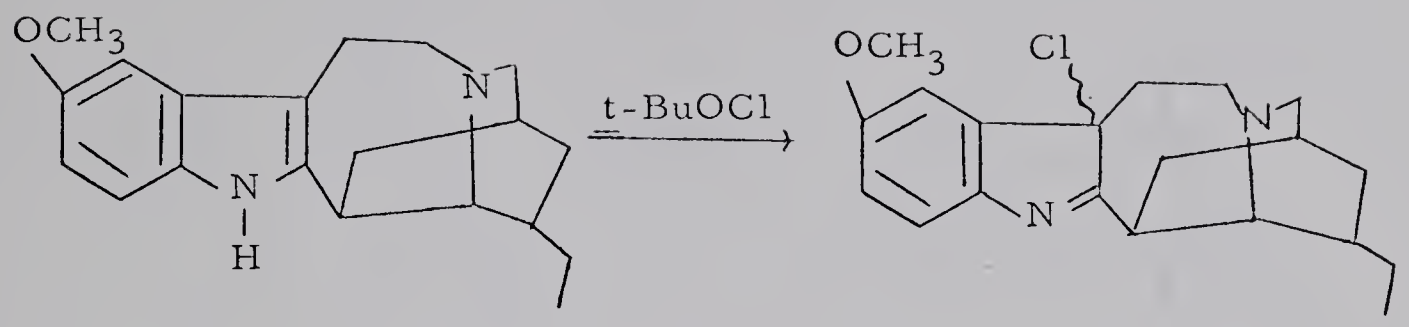
applied to the O-acetyl derivative 87 but the 7-acetoxy derivative 92 was not obtained. No effort was made to investigate the failure of this



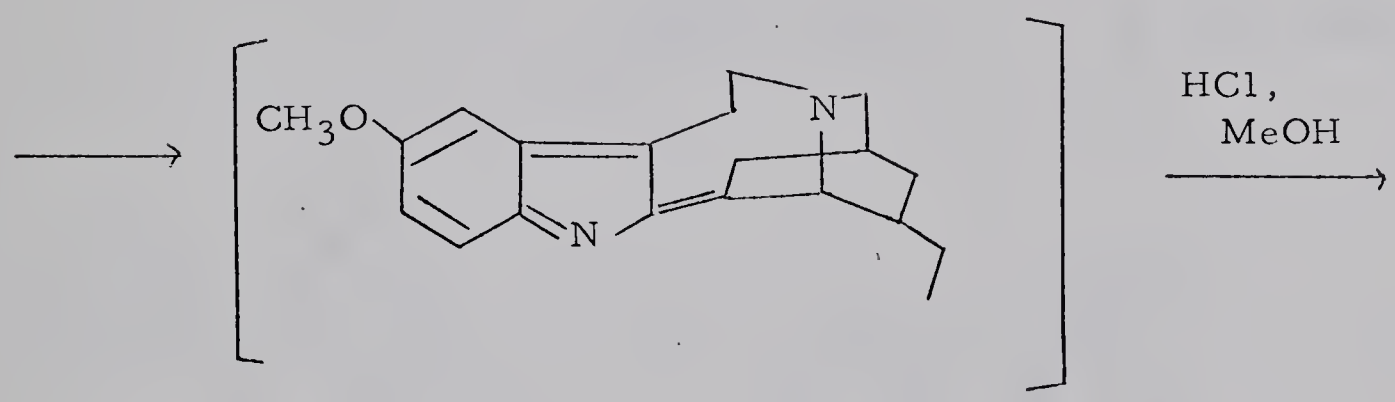
87 92

reaction and at this stage of the work the detailed procedure for such a cleavage was not available.

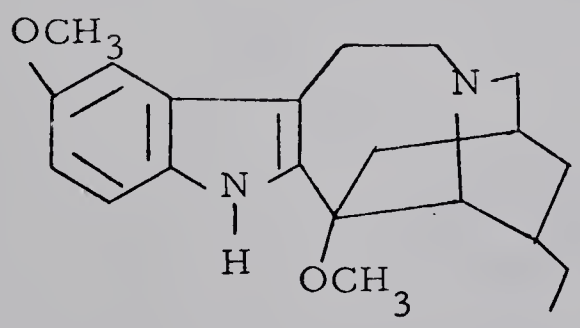
Buchi and Manning[33] reported a method for introduction of functional groups at the C_{18} position of ibogaine (93) which is equivalent to C_3 of the O-acetyl compound 87. The method is outlined in Scheme VIII and was applied to compound 87 as shown in Scheme IX. Reaction of 87 with t-butyl-hypochlorite provided chloroindolenine (97) in quantitative yield. The latter when treated with hydrogen chloride in methanol



93 94

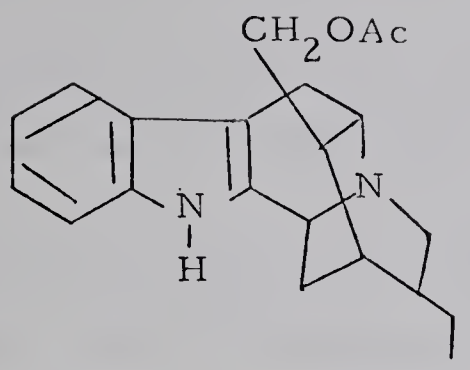


95

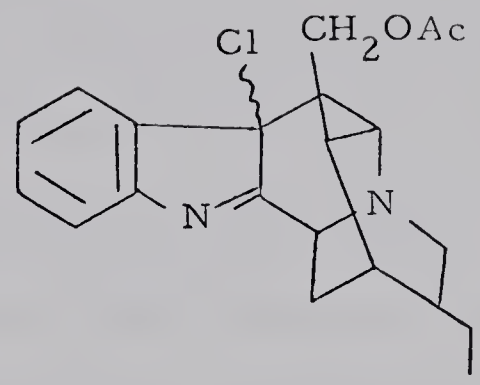


96

SCHEME VIII



87



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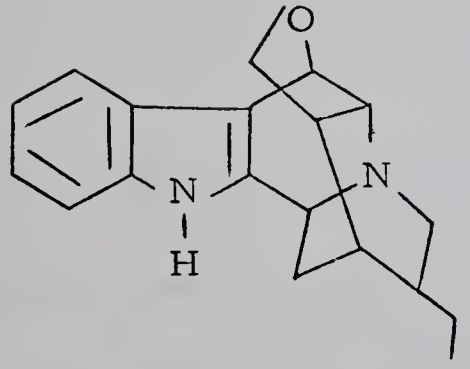

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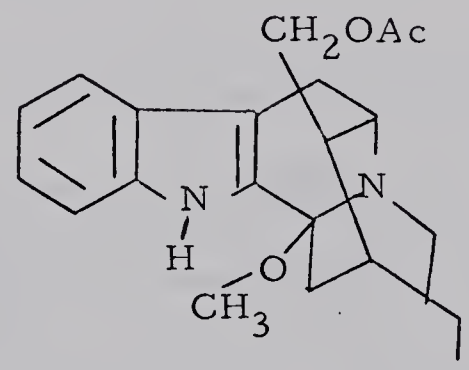
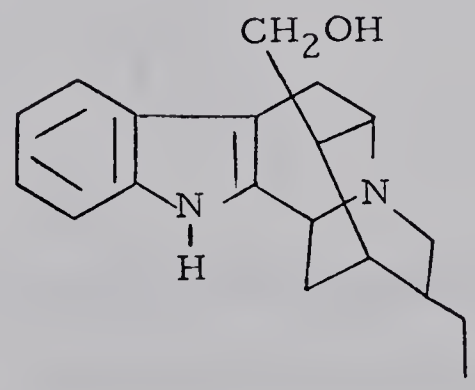


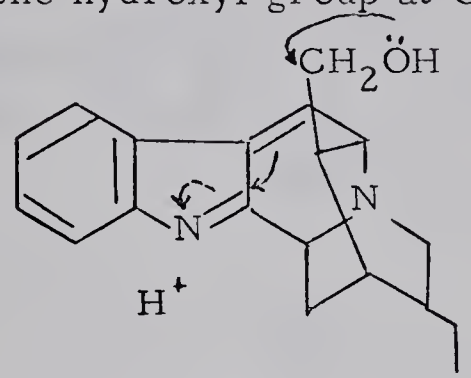
98



86

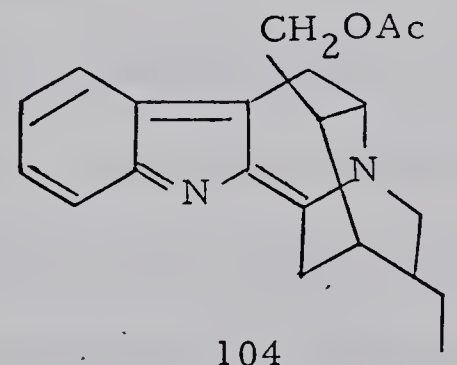
SCHEME IX

provided crystalline material whose nmr spectrum (60°, 100 mc, figure 6) showed the absence of a methoxyl group and the presence of a doublet at τ 4.5 which can be assigned to  of compound 99 and a mass spectrum showing a peak at m/e 294. These spectral data were compatible with structure 99 instead of the desired compound 98. Further proof of this compound was achieved by reduction of 99 with lithium aluminum hydride affording the starting material 86. Compound 99 was possibly formed by an elimination of hydrogen chloride followed by a nucleophilic attack of the hydroxyl group at C_6 forming a five membered



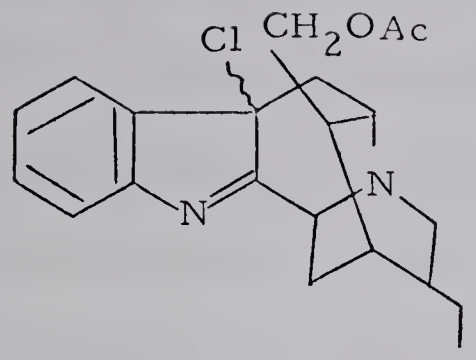
105

ring ether as shown in (105). The failure to form 3-methoxy compound 98 was first attributed to failure of obtaining intermediate (104). A comparison of Drieding models of 95 and 104 revealed that there was



104

considerable strain in the molecule 104 and introduction of a double bond at C_2-C_3 may not be possible, instead an intermediate 105 may have been formed. This approach was then abandoned and another approach as outlined in Scheme X was followed.



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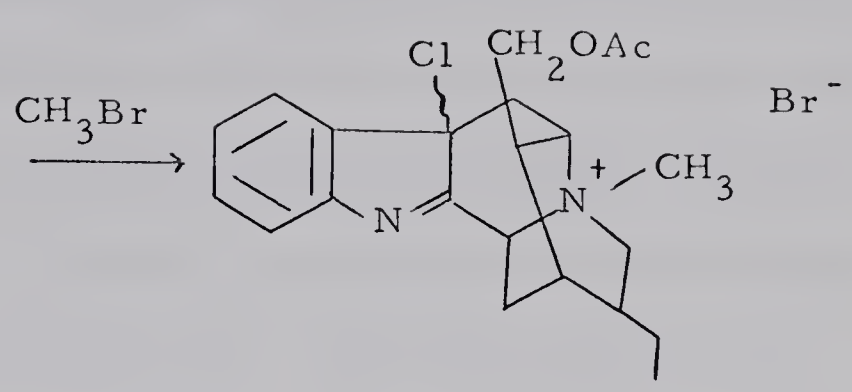

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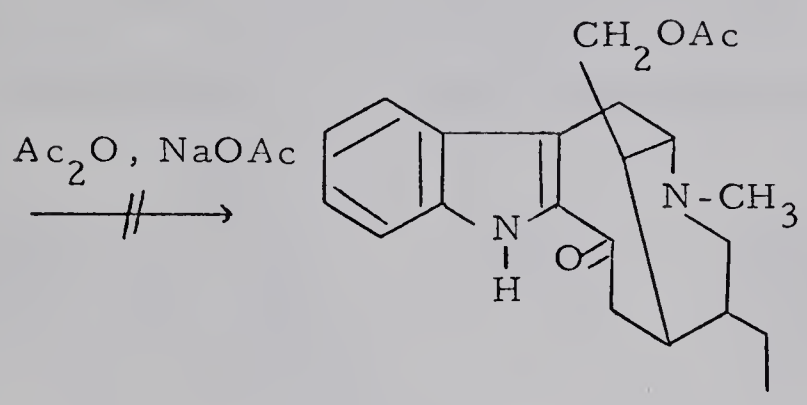
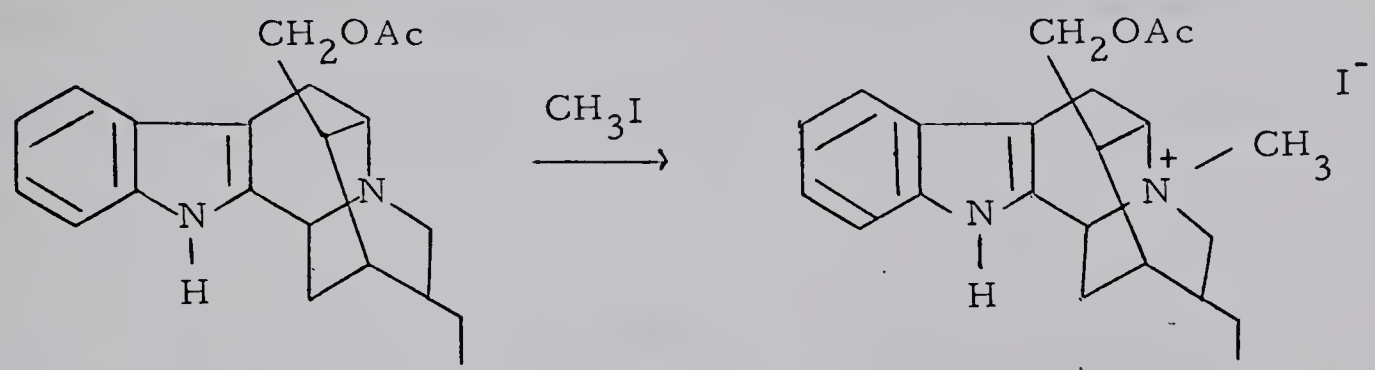


101

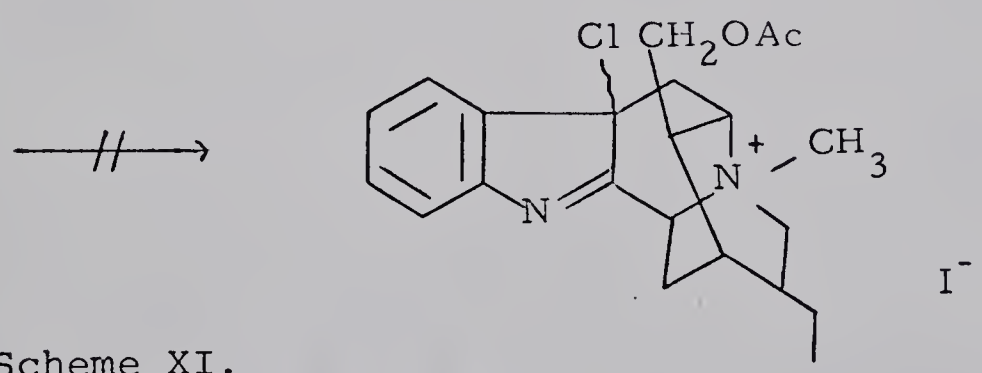
SCHEME X

This involved quarternization of N_b of 97 to facilitate C-D ring cleavage and also to form the required tertiary amine in the ten membered ring compound 101. However, these aims were not achieved. Reaction of the indolenine 97 with methyl bromide provided amorphous material whose infrared spectrum showed weak -C=N- stretching absorption compared to that of 97. This amorphous material could not be induced to crystallize and was further reacted as such with acetic anhydride and sodium acetate in the hope of achieving the last step of Scheme X. The material isolated from this reaction did not show the characteristic 2-acylindole absorption

in the infrared spectrum (1645 cm^{-1}). On the basis of this result, structure 101 was ruled out, but the isolated material was not characterized. The indolenine 97 was found to be unstable at room temperature in chloroform solution or on silicic acid rearranging to an indole compound. It was then believed that under the reaction conditions for quarternization compound 100 was not obtained in pure form. There was partial if not total rearrangement as shown in the decrease in intensity of the -C=N- absorption in the infrared spectrum of 100. To avoid this unfavorable rearrangement, a modification of Scheme X was made as



96 102



shown in Scheme XI.

103

SCHEME XI

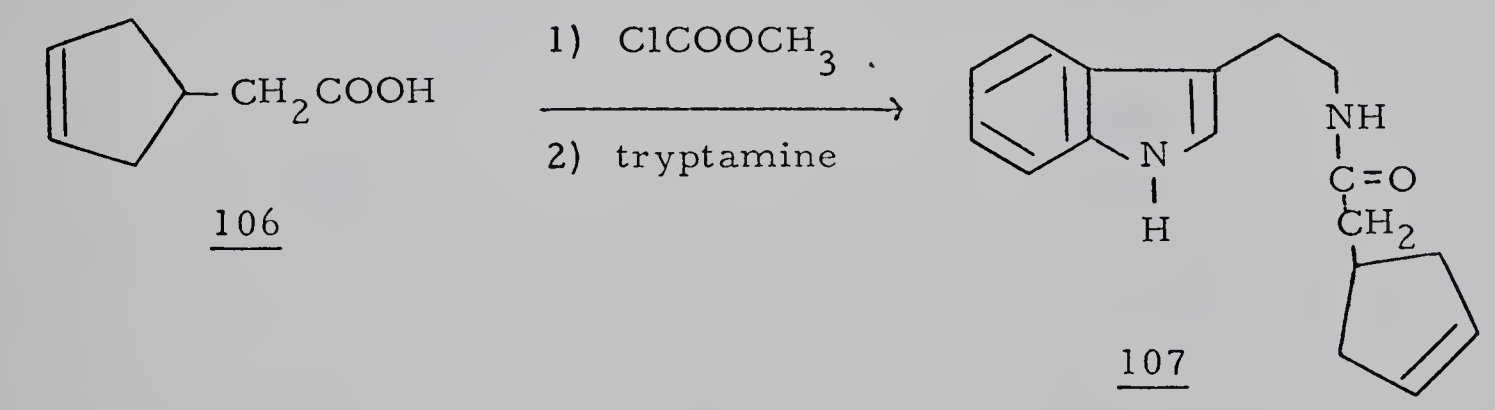
Reaction of acetate 96 with methyl idodide followed by oxidation with t-butyl hypochlorite afforded a compound which did not show absorption

that could be attributed to the quarternary $-\overset{|}{\underset{|}{N}}{}^{+}-CH_3$ protons in the nmr spectrum. Compound (103) was not obtained and this approach was abandoned.

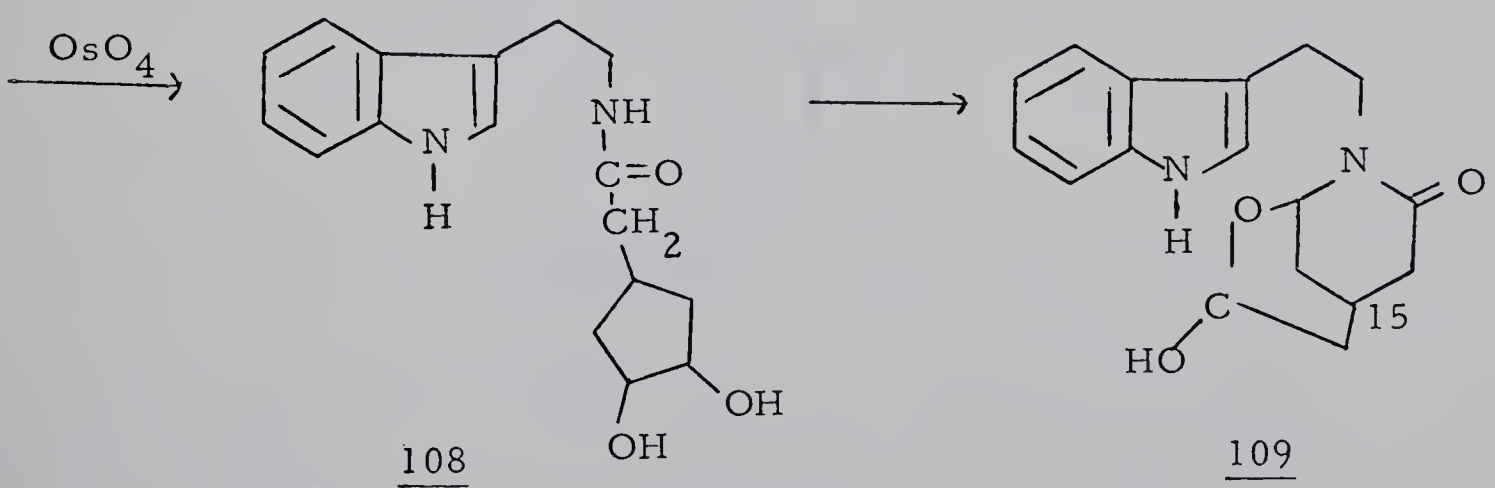
B - SYNTHESIS OF 2-(β-ACETOXY-ETHYL) 4-KETO, HEXAHYDRO-INDOLO (2, 3a) QUINOLIZINE 112

SYNTHESIS

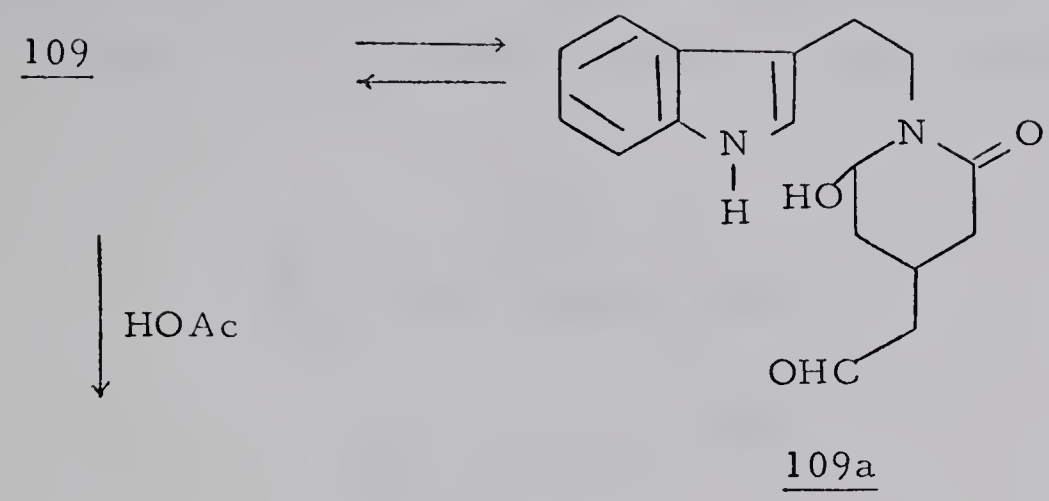
The unsuccessful approach to synthesis of 2-acylindole type compounds from ajmaline led us to develop a new synthetic scheme. This involved the synthesis of the title compound (112) as a possible intermediate in the synthesis of vobasine and its congeners. The scheme was projected as outlined below.



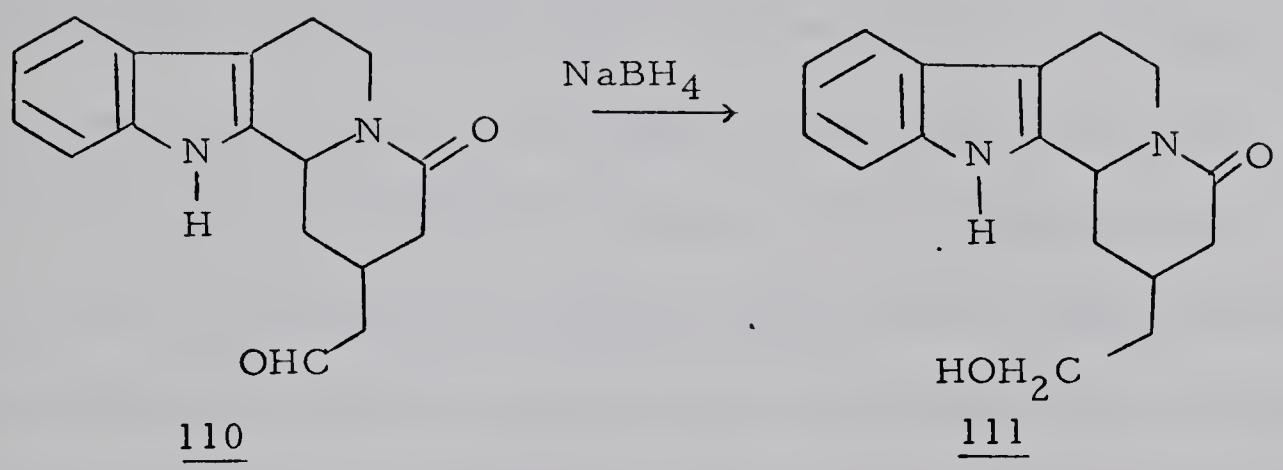
106 107



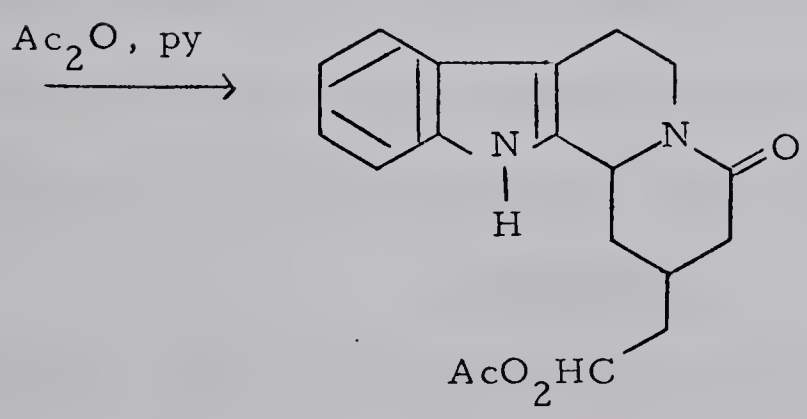
108 109



109a

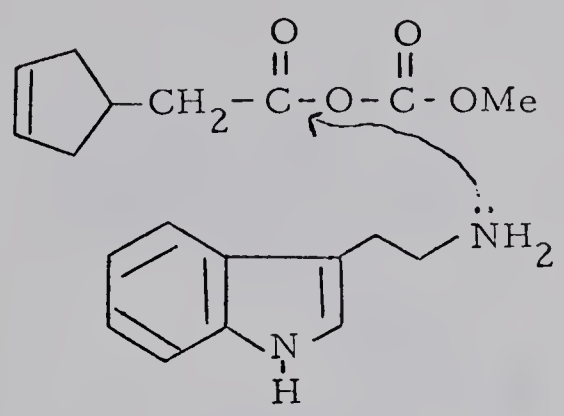


110 111



112

The mechanism suggested for the formation of amide (107) involved the formation of a mixed anhydride (113) followed by a nucleophilic attack of tryptamine as shown below. Reaction of 107 with osmium



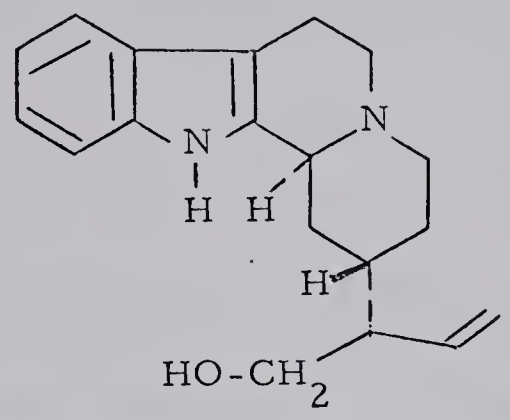
113

tetroxide afforded crystalline diol (108) which on oxidative cleavage with sodium periodate failed to give (109a) but provided a compound whose infrared spectrum indicated the absence of an aldehyde group. Preparation of a Drieding model of 109a revealed that the stereochemistry of the hydroxyl and the aldehyde groups were favourable for the formation of the hemiacetal (109). Reaction of 109 with aqueous acetic acid afforded the tetracyclic amide (110) in 70% yield. Reduction of 110 with sodium borohydride followed by acetylation gave the corresponding acetate (112). The stereochemistry at C_{15} was believed to be of the normal series where hydrogen was below the plane, since only one epimer was isolated.

COMMENTS

Recently, Johns and Lamberton[34] reported the elucidation of the structure of a new indole alkaloid, antirhine (115), isolated from Antirhea putaminosa, which was thought to be the parent member of a small group of indole alkaloids which possess a 15-β hydrogen.

Further work is being done by S. K. Sarkar towards the synthesis of antirhine to establish the structure of the synthetic intermediate 112 and finally toward the synthesis of vobasine.



115

EXPERIMENTAL

INSTRUMENTS

Unless otherwise indicated, infrared spectra were measured on Perkin-Elmer 21 infrared recording spectrometer in chloroform solution; the nmr spectra on a Varian Associates A-60 nuclear magnetic resonance spectrometer in deuterochloroform using tetramethylsilane as an internal standard; the ultraviolet spectra on a Perkin-Elmer 202 UV-VIS recording spectrophotometer in 95% ethanol and the mass spectra on an Associated Electrical Industries Ltd. Model MS-9 recording mass spectrometer, by a direct probe introduction of the sample; the melting points on Fisher-Johns Melting Point apparatus and were uncorrected.

The nmr spectra were determined by R. N. Swindlehurst, Miss S. Southern, G. Bigam and associates; the mass spectra by Dr. A. Hogg and Mr. A. Budd; elemental analyses were performed by Mrs. D. Mahlow and Mrs. A. Dunn.

CHROMATOGRAPHY

Column chromatography was used to separate and purify mixtures of compounds throughout the whole work. For compounds unstable to acid, neutral alumina (Woelm) was used as adsorbent, otherwise silicic acid (Mallinckrodt, 100 mesh) was used.

Thin layer chromatography was used mainly as a qualitative test of the purity of materials. The two kinds of adsorbents used were Silica Gel G (according to Stahl) and Aluminum Oxide G (RSCo.).

ISOLATION OF MATERIAL

The general procedure used for isolation of material was to dilute the reaction mixture with water followed by extraction with several portions of a suitable solvent, then washing of the combined extracts with saturated sodium chloride solution, drying over amorphous sodium sulfate and evaporation of the solvent under vacuum.

ACETYLATION

The general procedure used is as follows.

A solution of the starting material in an excess of a 1:1 mixture of pyridine and acetic anhydride was warmed at 50° for one hour.. The solution was evaporated *in vacuo* and the residue was treated with xylene and evaporated several times until no pyridine could be detected.

PURIFICATION OF MATERIALS

Crystalline materials were purified by recrystallizing with suitable solvents.

Materials that were viscous oils were purified by column chromatography and used as such.

PREPARATION OF AJMALINE OXIME 23

This compound was prepared as reported in the literature.[8] Ajmaline oxime 23 had mp 217-218° (lit.[8] mp 220°).

PREPARATION OF ANHYDROAJMALINE OXIME 24

This compound was prepared as reported in the literature.[8] Anhydroajmaline oxime 24 had mp 254-255° (lit.[8] mp 254-255°).

PREPARATION OF ANHYDRO-N_b-BENZOYLAJMALINE OXIME 25

Anhydroajmaline oxime 24 (900 mg, 2.8 mmoles) was dissolved in hot dioxane (50 ml). The solution was cooled to room temperature and 0.5 N NaOH (62 ml, 3.1 mmoles) and benzoyl chloride (0.36 ml, 3.1 mmoles) were added. After stirring for one hour the solution was partially concentrated and the residue partitioned between water (50 ml) and chloroform (200 ml). Isolation with chloroform provided 25 (1.02 g, 85%, mp 268-269° from acetone); ν_{max}^{nujol} 3330 (-OH), 2230 (-C≡N) and 1620 cm^{-1} (-N-C=O). Analysis: Calculated for $C_{27}H_{29}O_2N_3$: C, 75.85; H, 6.84; N, 9.83. Found: C, 75.53; H, 6.61; N, 9.74.

PREPARATION OF ANHYDRO-N_b-BENZOYLAJMALAL-OXIME A 19a

Anhydro-N_b-benzoylajmaline oxime 25 (1.5 g, 3.4 mmoles) was dissolved in hot methylene chloride (150 ml). The solution was cooled to room temperature and lead tetraacetate (1.5 g, 3.4 mmoles) was added and the mixture stirred for three minutes. Ice was added to the reaction mixture and the two layers were separated. The organic layer

was washed three times with an ice-water mixture, dried and evaporated to yield 19a (1.4 g, 93%, mp 219-220° from ethyl acetate); $\nu_{max}^{CHCl_3}$ 2700, 1725 (CHO), 1630 (-N-C(=O)-ϕ) cm^{-1} (see figure 7); nmr (see figure 4). Analysis: Calculated for $C_{26}H_{27}O_2N_3$: C, 76.0; H, 6.0; N, 9.9. Found: C, 75.94; H, 6.08; N, 9.31.

PREPARATION OF ANHYDRO-N_b-BENZOYLAJMALAL OXIME B 19b

Anhydro-N_b-benzoylajmaline oxime 25 (500 mg, 1.1 mmoles) was dissolved in hot methylene chloride (50 ml). The solution was cooled to room temperature and lead tetraacetate (570 mg, 1.2 mmoles) was added and the mixture stirred for five minutes. The solution was adsorbed on alumina (25 g, activity III) and elution with methylene chloride yielded 19b (423 mg, 85%); $\nu_{max}^{CHCl_3}$ 2700, 1725 (CHO), 2230 (-C≡N), 1630 (-N-C(=O)-) cm^{-1}; nmr (see figure 5).

PREPARATION OF ANHYDRO-N_b-METHYLAJMALINE OXIME 26

Anhydroajmaline oxime 24 (1 g, 3 mmoles) was refluxed with methyl iodide (20 ml), dry acetone (50 ml) and anhydrous potassium carbonate (10 g) for 2 hours. The solution was filtered, the residue washed with hot acetone and the combined filtrates were evaporated. The residue was basified with 15% aqueous ammonia to pH 9-10 and isolation with chloroform afforded an amorphous material 26 (1 g, 100%); $\nu_{max}^{CHCl_3}$ 3600, 3450 (-OH), 2225 (-C≡N), 1610 (aromatic) cm^{-1}; nmr τ 2.5-3.5 (aromatic protons), 6.0 (singlet, $-N_a-C-C\underline{H}-$), 7.34 (singlet, $-N_a-C\underline{H}_3$), 7.54 (singlet, $-N_b-C\underline{H}_3$), 8.9 (triplet, $-CH_2C\underline{H}_3$).

PREPARATION OF ANHYDRO-N_b-METHYLAJMALAL OXIME 27

Lead tetraacetate (2.7 g, 6 mmoles) was added to 26 (2 g, 5.9 mmoles) in methylene chloride (100 ml) and the mixture was stirred for 5 minutes at room temperature under nitrogen. The solution was adsorbed on alumina (80 g, activity III) and elution with methylene chloride yielded 27 as viscous oil (2 g, 100%); $\nu_{max}^{CHCl_3}$ 2700, 1730 (CHO), 2230 (C≡N) cm^{-1}; nmr τ 0.33 (singlet, -CHO), 2.55-3 (multiplet, aromatic protons), 6.0 (singlet, N_a-C-CH-), 6.4 (singlet, $-N_a-CH_3$), 7.58 (singlet, $-N_b-CH_3$), 9.0 (triplet, $-CH_2-CH_3$).

PREPARATION OF ANHYDRO-N_b-METHYLAJMALOL OXIME 43

Sodium borohydride (2.5 mg, 0.69 mmoles) in methanol (2 ml) was added to 27 (157 mg, 0.46 mmole) in methanol (30 ml) and the mixture stirred at 10° for 1.75 hours. The solution was neutralized with carbon dioxide and water to pH 7 and partially concentrated in vacuo at 30°. Isolation with methylene chloride provided crude 43 (148 mg, 94%, mp 180-200°). Recrystallization from acetone raised the melting point to 210-212°. Analysis: Calculated for $C_{21}H_{27}ON_3$: C, 74.77; H, 8.0; N, 12.46. Found: C, 74.88; H, 7.62; N, 12.71.

PREPARATION OF ANHYDRO-N_b-METHYL-17-O-ACETYLAJMALOL OXIME 44

This compound was prepared from 43 as described on p. 61. 44 was obtained in quantitative yield (mp 157-159°); $\nu_{max}^{CHCl_3}$ 2230 (-C≡N), 1740 (-C(=O)-O-) cm^{-1}; nmr τ 2.5-3 (multiplet, aromatic protons), 5.93 (singlet, $-N_a-C(=O)-CH-$); 6.04 (singlet, $-CH_2-O-C(=O)-$), 6.4 (singlet, $-N_a-CH_3$), 7.59 (singlet, $-N_b-CH_3$), 7.95 (singlet, $-O-C(=O)-CH_3$) and 8.95

(triplet, $-CH_2-C\underline{H}_3$).

PREPARATION OF ANHYDRO-N_b-CARBOMETHOXY-17-O-ACETYL-AJMALOL OXIME 45

A solution of 44 (3.27 g, 8.8 mmoles) in acetone (100 ml) containing freshly distilled methyl chloroformate (8.27 g, 8.8 mmoles) was allowed to stand at room temperature for 2 hours. The solvent was evaporated and the residue was dissolved in chloroform. The chloroform solution was washed successively with 5% sodium bicarbonate, and saturated sodium chloride solution, dried and evaporated. The residue obtained was treated with methyl chloroformate (8.27 g, 88 mmoles) four times, following the procedure described above, unitl a strong -N-C=O absorption was obtained in the infrared spectrum. After chromatography on silicic acid 3.47 g (91%) of 45 was isolated as viscous oil; $\nu_{max}^{CHCl_3}$ 2230 (-C≡N), 1740 ($-\underset{\underset{O}{\|}}{C}-O-$), 1690 cm^{-1} ($-N-\underset{\underset{O}{\|}}{C}-O-$); nmr τ 2.5-2.9 (multiplet, aromatic protons), 4.5 (broad singlet, $-N_a-C-C\underline{H}-$), 5.2 (Broad singlet, $-N_b-C\underline{H}-CH-CH_2-OAc$), 6.0 (doublet, $-C\underline{H}_2-O-\underset{\underset{O}{\|}}{C}-$), 6.35 (singlet, $-N_a-C\underline{H}_3$), 6.42 (singlet, $-O-C\underline{H}_3$), 8.0 (triplet, $-CH_2-C\underline{H}_3$).

PREPARATION OF ANHYDRO-N_b-CARBOMETHOXYAJMALOL OXIME 46

Anhydro-N_b-carbomethoxy-17-O-acetylajmalol oxime 45 (1.46 g, 3.4 mmoles) was refluxed with 0.488 N NaOH in methanol (20 ml) for 10 minutes. The solution was then neutralized with carbon dioxide and water. Isolation with methylene chloride provided 46 (1.13 g, 86%, mp 230-232° from methanol); $\nu_{max}^{CHCl_3}$ 3500, 3400 (-OH), 2230 (-C≡N), 1690

(-N-C=O) cm^{-1}; calculated molecular weight for $C_{22}H_{27}O_3N_3$ 381; found m/e 381.

PREPARATION OF 21-O-BENZOYLAJMALINE 31.

This compound was prepared as described in the literature.[19] The product gave mp 219° (lit.[19] mp 219°).

PREPARATION OF BENZOYLAJMALAL-A 32

FIRST METHOD[10]

Lead tetraacetate (306 mg, 0.69 mmole) was added to a solution of 21-O-benzoylajmaline 31 (270 mg, 0.63 mmole) in benzene (15 ml) at room temperature in nitrogen atmosphere. After stirring for 5 minutes, the reaction mixture was diluted with ice water and the organic layer separated. Isolation with benzene provided benzoylajmalal-A 32 (210 mg, 78%, mp 191°); $\nu_{max}^{CHCl_3}$ 2930, 2700 and 1710 (CHO), 1722 (ester carbonyl), 1610, 1600 and 1580 (aromatic) cm^{-1}.

SECOND METHOD[19]

Lead tetraacetate (2.2 g, 4.9 mmoles) was added to a solution of 21-O-benzoylajmaline 31 (2 g, 4.6 mmoles) in methylene chloride (90 ml) at room temperature in nitrogen atmosphere and the mixture was stirred for 5 minutes. The solution was adsorbed on alumina (80 g, activity III) and elution with methylene chloride yielded 32 (1.69 g, 84%, mp 195-197°, from benzene-hexane) identical with the above product. Analysis: Calculated for $C_{27}H_{28}O_3N_2$: C, 75.67; H, 6.59; N, 6.54. Found: C, 75.07; H, 6.20; N, 6.32.

PREPARATION OF 21-O-BENZOYLAJMALOL-A 34

To a solution of 21-O-benzoylajmalal-A 32 (1 g, 2.3 mmoles) in methanol (240 ml) at 10° was added a solution of sodium borohydride (96 mg, 2.5 mmoles) in methanol (5 ml) and the mixture was stirred for 1.75 hours under nitrogen. The excess sodium borohydride was decomposed with carbon dioxide and water. The resulting solution was partially concentrated below 30° in vacuo. Isolation with methylene chloride yielded 34 (741 mg, 74%, mp 221-222°). Recrystallization from methanol provided pure material mp 228-230° dec. $\nu_{max}^{CHCl_3}$ 3400 (-OH) and 1722 cm^{-1} (-C=O).

PREPARATION OF AJMALOL-A 35

21-O-Benzoylajmalol-A 34 (988 mg, 2.3 mmoles) in absolute methanol (10 ml) and 2.5 N $NaOCH_3$ in methanol (1 ml) was warmed at 55° for 15 minutes with stirring. The solution (pH 10) was neutralized with wet carbon dioxide and evaporated. The residue was partitioned between water (5 ml) and methylene chloride (50 ml). Isolation with methylene chloride followed by chromatography on silicic acid afforded 35 (700 mg, 93%) as viscous oil; $\nu_{max}^{CHCl_3}$ 3550, 3300 (-OH) cm^{-1}.

PREPARATION OF AJMALOLACETAL-A 37

Hydrogen chloride was bubbled into a solution of ajmalol-A 35 (2.09 g, 6.5 mmoles) in absolute methanol (50 ml) for 5 minutes and the resulting solution warmed at 55° for 30 minutes. The solution was basified with solid sodium bicarbonate and water (20 ml) was then added. Methanol was evaporated from the reaction mixture and the

residue partitioned between water (100 ml) and chloroform (100 ml). The aqueous layer was extracted with several portions of chloroform and the combined extracts washed with sodium bicarbonate and water, then dried and evaporated yielding 37 (2.0 g, 100%) as viscous oil; $\nu_{max}^{CHCl_3}$ 3200 (-NH), 1610, 1585 (aromatic).

PREPARATION OF N_b-BENZOYLAJMALOL ACETAL-A 38

Ajmalol acetal-A 37 (2.1 g, 6.2 mmoles) in pyridine (5 ml) and benzoyl chloride (0.82 ml, 6.9 mmoles) were stirred at room temperature for 30 minutes. An ice-water mixture (100 ml) and chloroform (150 ml) were added and the organic layer was separated. The organic layer was washed successively with cold 1.5 N HCl (260 ml), 5% sodium bicarbonate and water, then dried and evaporated to yield 38 (2.62 g, 96%) as viscous oil; $\nu_{max}^{CHCl_3}$ 1620 (—N—C=O) cm^{-1}.

PREPARATION OF N_b-BENZOYLAJMALOL HEMIACETAL-A 39

A solution of N_b-benzoylajmalol acetal 38 (2.62 g, 5.9 mmoles) in dioxane (40 ml) containing 0.5 N HCl (20 ml) was refluxed for 20 minutes. The solution was basified with5% sodium bicarbonate (20 ml) and concentrated. The residue was partitioned between water (40 ml) and chloroform (150 ml). The chloroform layer was washed successively with 5% sodium bicarbonate and water, then dried and evaporated to give crude 39 (2.5 g, 100%). The crude material was chromatographed on silicic acid (100 g) and elution with chloroform afforded the compound as viscous oil; $\nu_{max}^{CHCl_3}$ 3580, 3350 (-OH), 1620 (-N-C=O) cm^{-1}; nmr τ 2.6-2.85 (multiplet, aromatic protons), 3.9 (singlet,

-N_a-C-C<u>H</u>-), 4.95 (singlet, -N_b-C<u>H</u>-CH_2-O-), 5.9 (broad, -C<u>H</u>$_2$-O-), 6.32 (singlet, -N_a-C<u>H</u>$_3$), 9.25 (triplet, -CH_2-C<u>H</u>$_3$).

PREPARATION OF N_b-BENZOYLAJMALOL OXIME-A 40

A solution of N_b-benzoylajmalol-hemiacetal 39 (440 mg, 1.03 mmoles) in absolute ethanol (10 ml) containing hydroxylamine hydrochloride (500 mg, 7.2 mmoles) and pyridine (1 ml) was refluxed for 3 hours. The solution was cooled, partially concentrated and the residue extracted with methylene chloride. The organic extract was washed successively with sodium bicarbonate solution and water, then dried and evaporated. The excess pyridine was removed as usual. The yield was 376 mg of 40 (83%, mp 237-238° from methanol); $\nu_{max}^{CHCl_3}$ 3600, 3300 (-OH) and 1620 (-N-C=O) cm^{-1}.

PREPARATION OF ANHYDRO-N_b-17-O-DIBENZOYLAJMALOL OXIME-A 41

N_b-Benzoylajmalol oxime-A 40 (501 mg, 1.1 mmoles) in pyridine (5 ml) and benzoyl chloride (0.44 ml, 3.85 mmoles) was stirred at 0° for 20 minutes, at room temperature for one hour and refluxed for 30 minutes. The reaction mixture was diluted with methylene chloride, washed successively with water, 1.5 N HCl, 5% sodium bicarbonate and water, then dried and the solvent was evaporated. Adsorption of the crude product on silicic acid (40 g) and elution with chloroform gave compound 41 (542 mg, 90%) as a viscous oil and used as such. Thin layer chromatography showed the presence of a single component; $\nu_{max}^{CHCl_3}$ 2230 (-C≡N), 1720 (-C=O), 1625 (-N-C=O) cm^{-1}.

PREPARATION OF ANHYDRO-N_b-BENZOYLAJMALOL OXIME-A 42

Anhydro-17-O-N_b-dibenzoylajmalol oxime-A 41 (348 mg, 0.65 mmole) in absolute methanol (4 ml) containing 2.5 N $NaOCH_3$ in methanol (0.5 ml) was warmed at 55° for 20 minutes. The solution was cooled and neutralized with carbon dioxide and water, concentrated and isolated with methylene chloride. Adsorption of the crude product on silicic acid (15 g) and elution with chloroform afforded 42 (276 mg, 99%) as viscous oil and used as such; $\nu_{max}^{CHCl_3}$ 3580, 3350 (-OH), 2230 (-C≡N), 1620 (-N-C=O) cm^{-1}.

PREPARATION OF ANHYDRO-N_b-BENZOYLAJMALAL OXIME-A 19a from 42

A solution of anhydro-N_b-benzoylajmalol oxime-A 42 (234 mg, 0.54 mmole) in dimethylsulfoxide (2 ml) and acetic anhydride (535 mg, 5.25 mmoles) was allowed to stand at room temperature overnight. The solution was concentrated and the excess acetic anhydride was removed as usual. Isolation with chloroform afforded crude material 19a. Adsorption of the crude material on silicic acid (20 g) gave a viscous oil which later crystallized (180 mg, 77% mp 220°); $\nu_{max}^{CHCl_3}$ 2700, 1730 (CHO), 1630 (-N-C(=O)-Φ) cm^{-1}.

PREPARATION OF ANHYDRO-N_b-BENZOYLAJMALOL OXIME-B 42a

To a solution of anhydro-N_b-benzoylajmalal oxime-B 19b (312 mg, 0.75 mmoles) in methanol (60 ml) at 10° was added a solution of sodium borohydride (32.8 mg, 0.88 mmoles) in methanol (1 ml) and the mixture stirred at 10° for 1.75 hours. The solution was neutralized with carbon dioxide and water, then partially concentrated. Isolation with methylene

chloride followed by adsorption of the crude product on alumina (activity III, 10 g) and elution with chloroform afforded 42a (311 mg, 100%) as viscous oil and used as such; $\nu_{max}^{CHCl_3}$ 3580, 3350 (-OH), 2230 (-C≡N), 1620 (-N-C=O) and 970 cm^{-1} (absent in 42).

PREPARATION OF ANHYDRO-N_b-17-O -DIBENZOYLAJMALOL OXIME-B 41a

To a solution of anhydro-N_b-benzoylajmalol oxime-B 42a (206 mg, 0.47 mmole) in pyridine (2 ml) at 0° was added benzoyl chloride (0.1 ml) and stirred for 40 minutes. The reaction mixture was poured into an ice-water mixture (5 ml) and extracted with chloroform. The organic layer was washed successively with sodium bicarbonate and water, dried and evaporated. The excess pyridine was removed as usual and the crude product was adsorbed on silicic acid. Elution with chloroform provided 41a (223 mg, 88%) as viscous oil; $\nu_{max}^{CHCl_3}$ 2240 (-C≡N), 1725 (-O-C(=O)-ϕ), 1630 (-N-C(=O)-ϕ).

PREPARATION OF ANHYDRO-N_b-17-O-DIACETYLAJMALINE OXIME 49

This compound was prepared from anhydroajmaline oxime 24 as described on page 61. The crude product was adsorbed on silicic acid and elution with chloroform yielded 49 (100%) as viscous oil ; $\nu_{max}^{CHCl_3}$ 2230 (-C≡N), 1730 (-O-C(=O)-) and 1625 (-N-C(=O)-) cm^{-1}.

PREPARATION OF ANHYDRO-N_b-ACETYLAJMALINE OXIME 50

A solution of anhydro-N_b-17-O-diacetylajmaline oxime 49 (120 mg, 0.29 mmoles) in methanol (2 ml) containing 2.5 N $NaOCH_3$ in methanol (0.2 ml) was warmed at 55° for 10 minutes. The solution was cooled,

neutralized with carbon dioxide and water and evaporated. The residue was partitioned between water and chloroform. The chloroform layer was washed with water, dried and evaporated to yield an amorphous residue 50; $\nu_{max}^{CHCl_3}$ 3300 (-OH), 2230 (-C≡N), 1620 cm^{-1} (-N-C=O).

PREPARATION OF ANHYDRO-N_b-ACETYLAJMALAL OXIME-A 51

To a solution of anhydro-N_b-acetylajmaline oxime 50 (133 mg, 0.36 mmoles) in methylene chloride (20 ml) at room temperature was added lead tetraacetate (159 mg, 0.36 mmoles) and the mixture stirred for 5 minutes under nitrogen. Ice was added to the reaction mixture and the two layers separated. The organic layer was washed 3 times with ice-water mixture, dried and evaporated to yield 51 (100 mg, 75%) as viscous oil and used as such; $\nu_{max}^{CHCl_3}$ 2700, 1725 (-CHO), 2225 (-C≡N), 1640 (-N-C(=O)-Bz); nmr (see figure 2) τ 0.55 (singlet, CHO), 6.4 (singlet, $-N_a-CH_3$), 7.83 (singlet, $-C(=O)-CH_3$).

PREPARATION OF N_b-CARBOMETHOXY ALCOHOL-B-64a

To a solution of the amino alcohol-B 55a (1 g, 3.5 mmoles) in methylene chloride (20 ml) were added freshly distilled methyl chloroformate (1 g, 10.5 mmoles) in methylene chloride (3 ml) and triethylamine (1 g, 10.5 mmoles) in methylene chloride (3 ml). After stirring at room temperature for 1 hour, the reaction mixture was poured into an ice-water mixture (20 ml) and extracted with methylene chloride. The extract was washed successively with cold 1 N HCl, cold 5% sodium bicarbonate and water then dried and evaporated to give 64a (1.1 g, 91%, mp 139-140° from ethyl acetate); $\nu_{max}^{CHCl_3}$ 3400, 3030 (-OH), 1690 cm^{-1}

(-N-C=O). Analysis: Calculated for $C_{20}H_{26}O_3N_2$: C, 70.15; H, 7.65; N, 8.18 mol. wt. 342. Found: C, 69.62; H, 7.6; mol. wt. 342 (mass spec).

PREPARATION OF N_b-CARBOMETHOXY ALCOHOL-A 64

This compound was prepared from 55 as described for N_b-carbomethoxy alcohol-B 64a. Compound 64 had mp 168-169°. The infrared spectrum was identical with that of 64a.

PREPARATION OF N_b-CARBOMETHOXY O-ACETATE 65

This compound was prepared from N_b-carbomethoxy alcohol-A 64 as described on page 61. The crude product was adsorbed on silicic acid and elution with chloroform afforded 65 (90%, mp 120-121° from ether); $\nu_{max}^{CHCl_3}$ 3400 (-NH), 1720 (-O-C(=O)-CH_3) and 1670 (-N-C(=O)-O-) cm^{-1}; nmr τ 3.15 (singlet, -N_a-CH=C-), 4.4 (doublet, -CH=CH-), 4.8 (doublet, NH-C(=O)-O-), 6.33 (singlet, -N_a-CH_3), 6.38 (singlet, -OCH_3), 7.9 (singlet, CH_3-C(=O)-O-). Analysis: Calculated for $C_{22}H_{28}O_4N_2$: C, 68.72; H, 7.34; N, 7.29. Found: C, 68.48; H, 6.98; N, 6.79.

PREPARATION OF N_b-CARBOMETHOXY O-ACETATE-B 65a

This compound was prepared from N_b-carbomethoxy alcohol-B 64a as described above for 65. The crude product was adsorbed on silicic acid and elution with chloroform afforded 65a (100%, mp 96-98° from ether). The infrared spectrum was identical with that of 65; nmr τ 3.14 (singlet, -N_a-CH-), 4.3 (singlet, -CH=CH-), 5.1 (doublet, NH-C(=O)-O-),

6.33 (singlet, $-N_a-C\underline{H}_3$), 6.45 (singlet, $-O-C\underline{H}_3$), 8.0 (singlet, $-O-\overset{O}{\overset{\|}{C}}-C\underline{H}_3$). Analysis: Calculated for $C_{22}H_{28}O_4N_2$: C, 68.72; H, 7.34; N, 7.29. Found: C, 68.39; H, 7.03; N, 6.6.

PREPARATION OF N_b-CARBOMETHOXY O-ACETYL DIOL-B 66a

Osmium tetroxide (736 mg, 2.9 mmoles) was added to a stirred solution of N_b-carbomethoxy O-acetate-B 65a (1.06 g, 2.7 mmoles) in dry THF (50 ml) at 0°. The solution was allowed to stand at 0° overnight. Hydrogen sulfide was bubbled into the reaction mixture for 30 minutes and the precipitate was removed by filtration through Celite. The filter cake was washed repeatedly with portions of boiling THF. The combined washings and filtrate were evaporated. The residue was adsorbed on silicic acid (50 g) and elution with 5% methanol in chloroform afforded the diol 66a (880 mg, 82%, mp 141-142°); $\nu_{max}^{CHCl_3}$ 3400 (-OH), 1720 (broad, $-NH-\overset{O}{\overset{\|}{C}}-$ and $-O-\overset{O}{\overset{\|}{C}}-$); nmr τ 6.33 (singlet, $-N_a-C\underline{H}_3$), 6.45 (singlet, $-O-C\underline{H}_3$), 8.0 (singlet, $-O-\overset{O}{\overset{\|}{C}}-C\underline{H}_3$). Analysis: Calculated for $C_{22}H_{30}O_6N_2$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.04; H, 6.90; N, 6.74.

PREPARATION OF N_b-CARBOMETHOXY O-ACETYL DIOL-A 66

This compound was prepared from N_b-carbomethoxy O-acetyl-A 65 as described above for diol-B 66a. The crude material was adsorbed on silicic acid and elution with 5% methanol in chloroform provided amorphous material 66 (100%) whose infrared spectrum was identical with that of 66a.

PREPARATION OF N_b-CARBOMETHOXY O-ACETYL ALDEHYDE-A 67

Sodium metaperiodate (64 ml of 0.1 M sodium metaperiodate in 50% methanol-water solution, 6.4 mmoles) was added to a solution of N_b-carbomethoxy O-acetyl diol-A 66 (2.42 g, 5.8 mmoles) in methanol (30 ml) and water (15 ml) and the mixture allowed to stand overnight at room temperature. The mixture was filtered and the filtrate partially concentrated. The residue was extracted with methylene chloride and the extract washed successively with 5% sodium bicarbonate solution and water, then dried and evaporated to yield amorphous material 67 (2.1 g, 90%) and used as such; $\nu_{max}^{CHCl_3}$ 2700 (CHO), 1720 (broad, CHO, -N-C=O, -O-C=O).

PREPARATION OF N_b-CARBOMETHOXY O-ACETYL ALDEHYDE-B 67a

This compound was prepared from N_b-carbomethoxy O-acetyl diol-B 66a as described above for aldehyde-A 67. Compound 67a was obtained in 91% yield as amorphous material and showed an infrared spectrum identical with that of 67.

PREPARATION OF TETRACYCLIC ALDEHYDE-B 68a

N_b-Carbomethoxy O-acetyl aldehyde-B 67a (140 mg, 0.33 mmoles) in glacial acetic acid (4 ml) and water (1 ml) was warmed at 50° for 2 hours. The solution was concentrated in vacuo. The residue was diluted with water and extracted with methylene chloride. The extract was washed successively with 5% sodium bicarbonate and water, then dried and evaporated. The crude residue was adsorbed on silicic acid and elution with chloroform afforded 68a (67 mg, 50%) as viscous oil and used as such;

$\nu_{max}^{CHCl_3}$ (see figure 8) 2700 (-CHO), 1725 (-CHO, -O-C=O), 1690 (-N-C=O) cm^{-1}; nmr τ 0.5 (singlet, C<u>H</u>O), 4.6 (triplet, $-N_b-C\underline{H}-C=C-$), 5.4 ($-N_b-C\underline{H}-CH-CH_2-OAc$), 5.9 (doublet, $-C\underline{H}_2-Oac$), 6.32 (singlet, $-N_b-C\underline{H}_3$), 6.42 (singlet, $-OC\underline{H}_3$), 7.95 (singlet, $-O-\underset{\underset{O}{\|}}{C}-C\underline{H}_3$).

PREPARATION OF TETRACYCLIC ALDEHYDE-A 68

This compound was prepared from N_b-carbomethoxy O-acetyl aldehyde-A 67 as described above for acetate-B 68a. The crude product was adsorbed on silicic acid and elution with chloroform afforded in 60% yield 68as viscous oil, whose infrared spectrum was similar to that of 68a; nmr is shown in figure 3.

PREPARATION OF TETRACYCLIC ALCOHOL-A 69

A solution of tetracyclic aldehyde-A 68 (112 mg, 0.26 mmole) in dry THF (8 ml) and stock lithium aluminum hydride-THF solution (0.75 M 1.3 ml, 1.04 mmoles) was stirred at room temperature for one-half hour under nitrogen. The excess lithium aluminum hydride was decomposed with wet THF and the mixture was filtered through Celite. The filter cake was washed with several portions of boiling THF. The combined washings and filtrate were evaporated. The crude material was adsorbed on alumina (activity III, 10 g) and elution with 5% methanol in chloroform afforded 69 (84 mg, 100% mp 192-194° from benzene-chloroform). Analysis: Calculated for $C_{19}H_{22}O_2N_2$: C, 72.58; H, 8.34; N, 8.91; mol. wt. 314. Found: C, 72.61; H, 8.09; mol. wt. 314 (mass spec).

PREPARATION OF TETRACYCLIC ALOCHOL-B 69a

This compound was prepared from tetracyclic aldehyde-B 68a as described above for alcohol-A 69. Compound 69a was obtained in 70% yield (mp 156-158° from ethyl acetate); $\nu_{max}^{CHCl_3}$ 3500, 3300 (-OH). Calculated molecular weight for $C_{19}H_{22}O_2N_2$ 314. Found m/e 314 (mass spec).

PREPARATION OF 21-DEOXYAJMALINE 14

This compound was prepared from ajmaline in two steps as reported in the literature.[8]

PREPARATION OF 21-DEOXYAJMALINE 17-O-ACETATE 83

This compound was prepared from deoxyajmaline 14 as described on page 61. The crude material was adsorbed on silicic acid and elution with chloroform afforded 83 (100%, mp 98, lit.[20] 102-108°); $\nu_{max}^{CHCl_3}$ 1720 (-O-C(=O)-CH_3).

PREPARATION OF 1-DEMETHYL-Δ'-21-DEOXYAJMALINE 17-O-ACETATE 84

This compound was prepared from 83 as described in the literature.[20] Compound 84, mp 178-179° was obtained in 50% yield; $\nu_{max}^{CHCl_3}$ 1730 (-O-C=O), 1620 (aromatic) and 1600 (-C=N-) cm^{-1}; nmr τ 5.0 (singlet, -CH-OAc), 5.9 (multiplet, $-N_a=C-CH-N_b$), 7.85 (singlet, -O-C(=O)-CH_3); $\lambda_{max}^{95\%\ EtOH}$ 220 (ε 1.8×10^4) and 268 (ε 7×10^3) mu.

PREPARATION OF N_a-DESMETHYL-21-DEOXYAJMALOL-A 86

To a solution of 1-desmethyl-Δ'-21-deoxyajmaline 17-O-acetate 84

(1.2 g, 3.5 mmoles) in dry THF (25 ml) at 0° was added 0.75 M $LiAlH_4$ in THF (7 ml) and the mixture was stirred for 10 minutes. The excess $LiAlH_4$ was decomposed with wet THF and the precipitate was removed by filtration through Celite. The filter cake was washed with several portions of boiling THF and the combined filtrates evaporated. The crude residue was recrystallized from acetone affording 86 (900 mg, 90%, mp 227-230°); ν_{max}^{nujol} 3200, 3050 (-OH); $\lambda_{max}^{95\% EtOH}$ 203 (ε 1.3×10^4), 227 (ε 2.4×10^3), 271 (ε 5×10^3), 283 (ε 5×10^3) mu.

PREPARATION OF N_a-DESMETHYL-21-DEOXYAJMALOL-17-O-ACETATE-A 87

This compound was prepared from 86 as described on page 61. The crude material was adsorbed on silicic acid and elution with 2% methanol in chloroform gave 87 (50%) and diacetate 88 (50%). Recrystallization of 87 from ethylacetate afforded pure material mp 215-217°; $\nu_{max}^{CHCl_3}$ 3400, 3300 (-NH), 1740 (-O-C(=O)-) cm^{-1}; nmr τ 8.05 (singlet, -O-C(=O)-CH_3).

PREPARATION OF 7-CHLOROINDOLENINE 97 [33]

To a cold solution (0°) of 87 (114 mg, 0.33 mmole) in methylene chloride (5 ml) containing triethylamine (33 mg, 0.045 ml) was added dropwise a solution of t-butyl hypochlorite (0.041 ml, 0.35 mmole) in carbon tetrachloride (2 ml) under nitrogen. After stirring for 40 minutes at 0°, the solution was washed with ice-water mixture, then dried and evaporated to afford 97 (120 mg, 100%); $\nu_{max}^{CHCl_3}$ 1730 (-O-C=O), 1590 (-C=N) cm^{-1}; nmr τ 5.8 (triplet, $-N_a=C-CH-N_b$), 6.3 (doublet, $-CH_2-OAc$, J = 8 cps), 8.2 (singlet, -O-C(=O)-CH_3), 9.1 (triplet, $-CH_2-CH_3$).

REACTION OF 7-CHLOROINDOLENINE 97 WITH 1% HCl IN METHANOL [33]

7-Chloroindolenine 97 (159 mg, 0.42 mmole) was refluxed with 1% HCl in dry methanol (5 ml) for 1 hour. The solution was cooled, basified with 10% sodium carbonate (6 ml) and diluted with methylene chloride. The organic layer was washed with water, then dried and evaporated to yield 99 (110 mg, 80%); $\nu_{max}^{CHCl_3}$ 3100 cm^{-1} (-NH-); nmr (100 mc, 60, figure 6); $\lambda_{max}^{95\%\ EtOH}$ 222 (ε 2.85×10^4), 272 (ε 4×10^3), 284 (ε 4×10^3), 292 (ε 3.5×10^3) mu. Calculated molecular weight for $C_{19}H_{22}N_2O$; 294. Found: m/e 294.

REDUCTION OF 99 WITH LITHIUM ALUMINUM HYDRIDE

To a solution of 99 (66 mg, 0.21 mmole) in dry THF (2 ml) was added 0.75 M $LiAlH_4$ in THF (1 ml, 0.75 mmole) and the mixture was stirred for 20 minutes at room temperature. The excess $LiAlH_4$ was decomposed with wet THF and the precipitate removed by filtration through Celite. The residue was washed with several portions of boiling THF and the combined filtrates evaporated. The crude material was recrystallized from ethyl acetate giving in quantitative yield 86, mp 225-228°, identical with N_a-desmethyl-21-deoxyajmalol-A 86.

PREPARATION OF DIETHYL - Δ^3-CYCLOPENTENYLMALONATE 114

This compound was prepared as described in the literature.[35] The condensed product 114 was obtained in 60% yield, bp 78°/0.01 mm Hg (lit.[35] bp 117-120° at 4 mm); nmr τ 4.5 (singlet, -CH=CH-), 5.9 (quartet, -O-CH_2-CH_3), 8.8 (triplet, -O-CH_2-CH_3).

PREPARATION OF Δ^3-CYCLOPENTENYLACETIC ACID 106

This compound was prepared from diethyl-Δ^3-cyclopentenylmalonate in two steps as described in the literature.[35]

PREPARATION OF AMIDE 107

To a cooled solution (-5°) of Δ^3-cyclopentenylacetic acid 106 (315 mg, 2.5 mmoles) in dry THF (5 ml) containing tri ethylamine (0.34 ml, 2.5 mmoles) was added dropwise ethyl chloroformate (270 mg, 2.5 mmoles) in dry THF (3 ml) under nitrogen. After stirring for 30 minutes, a solution of tryptamine (400 mg, 2.5 mmoles) in dry THF (3 ml) was added during 5 minutes. The solution was stirred for 90 minutes at -5°, 90 minutes at room temperature and refluxed for 15 minutes. Isolation with methylene chloride afforded the condensed product 107. The crude material was adsorbed on silicic acid and elution with chloroform provided pure 107 (553 mg, 83%, mp 108-109° from ethyl acetate); $\nu_{max}^{CHCl_3}$ 3500, 3300 (-NH), 1660 (-N-C=O) cm^{-1}; nmr 1.5 (singlet, $-N_a\underline{H}-$), 3.25 (singlet, $-N_a-C\underline{H}=C-$), 4.3 ($-N_bH-C=O$), 4.55 (singlet, $-C\underline{H}=C\underline{H}-$), 6.5 (quartet, $-C\underline{H}_2-NH-$). Analysis: Calculated for $C_{17}H_{20}ON_2$: C, 76.08; H, 7.51; N, 10.44. Found: C, 75.74; H, 7.37; N, 10.04.

PREPARATION OF DIOL 108

Osmium tetroxide (1.0 g, 3.9 mmoles) was added to a stirred solution of amide 107 (1.0 g, 3.7 mmoles) in dry THF (30 ml) at 0°. The solution was allowed to stand at 0° overnight. Hydrogen sulfide was bubbled into the reaction mixture for 30 minutes and the precipitate was

was removed by filtration through Celite. The filter cake was washed repeatedly with portions of boiling THF. The combined washings and filtrate were evaporated to yield 108 (1.0 g, 89%, mp 124-126°); ν_{max}^{nujol} 3400, 3300 (-OH, -NH), 1660 (-NH-C=O) cm^{-1}. Calculated molecular weight for $C_{17}H_{22}N_2O_2$: 302. Found: m/e 302.

PREPARATION OF DIALDEHYDE 109

Sodium metaperiodate (23 ml of 0.1 M $NaIO_4$ in 50-50 methanol-water solution, 2.3 mmoles) was added to a solution of diol 108 (700 mg, 2.3 mmoles) in methanol (20 ml) and water (10 ml) and the mixture allowed to stand overnight at room temperature. The mixture was filtered and the filtrate was partially concentrated. The residue was extracted with methylene chloride and the extract washed successively with 5% sodium bicarbonate solution and water, then dried and evaporated to yield 109 (529 mg, 76%) as viscous oil and used as such; $\nu_{max}^{CHCl_3}$ 3400 (-OH) cm^{-1}; nmr showed the absence of aldehyde proton absorption.

PREPARATION OF TETRACYCLIC ALDEHYDE 110

Dialdehyde 109 (150 mg, 0.5 mmoles) in glacial acetic acid (2 ml) and water (1 ml) was warmed at 50° for 2 hours. The solution was concentrated in vacuo, the residue was diluted with water and extracted with methylene chloride. The extract was washed successively with 5% sodium bicarbonate and water, then dried and evaporated. The crude product was adsorbed on silicic acid and elution with 1% methanol in chloroform yielded 110 (70%); $\nu_{max}^{CHCl_3}$ 3200 (-NH), 2700, 1720 (-CHO),

1625 (-N-C=O) cm^{-1}; nmr τ 0.3 (-CHO); $\lambda_{max}^{95\% EtOH}$ 224, 275, 285 and 291 mu.

PREPARATION OF TETRACYCLIC ALCOHOL 111

To a solution of tetracyclic aldehyde 110 (132 mg, 0.46 mmole) in methanol (20 ml) at 10° was added a solution of sodium borohydride (22.8 mg, 0.6 mmole) in methanol (2 ml). The reaction mixture was stirred at 10° under nitrogen for 1.75 hours. The solution was neutralized with carbon dioxide and water to pH 7-8, then concentrated. Isolation with methylene chloride afforded the crude product 111 (90 mg, 68%, mp 203-210°).

PREPARATION OF ACETATE 112

This compound was prepared from alcohol 111 as described on page 61. The crude material was adsorbed on silicic acid and elution with chloroform afforded 112 (98 mg, 95%, mp 226-227°); $\nu_{max}^{CHCl_3}$ 3500 (-NH), 1725 (CH_3C=O), 1626 (-N-C=O) cm^{-1}. Calculated molecular weight for $C_{20}H_{26}N_2O_2$: 326. Found: m/e 326.

UNSUCCESSFUL EXPERIMENTS:

REACTION OF 7-CHLOROINDOLENINE WITH METHYL BROMIDE

A solution of 7-chloroindolenine 97 (125 mg, 0.33 mmole) in chloroform (3 ml) containing excess methyl bromide was allowed to stand overnight at room temperature. The solvent was evaporated to yield an amorphous material (171 mg); $\nu_{max}^{CHCl_3}$ 3200, 2700, 1620, 1590 cm^{-1}.

REACTION OF THE ABOVE PRODUCT WITH ACETIC ACID AND SODIUM ACETATE [32]

The residue from above (171 mg) was refluxed with 10% aqueous acetic acid (5 ml) containing sodium acetate (150 mg) for 3 hours. The solution was cooled and basified with ammonia and ice to pH 10-11. Isolation with methylene chloride provided material (110 mg); $\nu_{max}^{CHCl_3}$ 3500, 3200, 1720, 1610 (weak) cm^{-1}; nmr showed the absence of N_b-C$\underline{H}_3$ protons absorption; $\lambda_{max}^{95\%\ EtOH}$ 222, 271, 282 and 289 mu.

PREPARATION OF 102

A solution of 96 (130 mg, 0.38 mmole) in chloroform (4 ml) containing excess methyl iodide was refluxed for 3 hours. The solvent was evaporated to afford 102; nmr (in deuterated acetone) τ 0.9 (singlet, -N$\underline{H}$), 4.6 (doublet, N_a-C=C$\underline{H}$-N_b), 6.7 (singlet, N_b-C$\underline{H}_3$), 8.13 (singlet, -O-$\underset{\underset{O}{\|}}{C}$-C$\underline{H}_3$), 9.1 (triplet, -$CH_2$-C$\underline{H}_3$). The nmr data were compatible with structure 102.

REACTION OF 102 WITH t-BUTYLHYPOCHLORITE

To a cold solution (0°) of 102 (80 mg, 0.18 mmole) in methylene chloride (5 ml) containing triethylamine (0.024, 0.18 mmole) was added t-butylhypochlorite (0.021 ml, 0.19 mmole) in carbon tetrachloride (2 ml) dropwise under nitrogen. After stirring for 40 minutes at 0°, the solution was washed with ice-water mixture, then dried and evaporated to afford material (80 mg); $\nu_{max}^{CHCl_3}$ 1740, 1600 (weak) cm^{-1}; nmr showed the absence of -N_b-CH_3 absorption; $\lambda_{max}^{95\%\ EtOH}$ 221, 271, 282, 290 mu.

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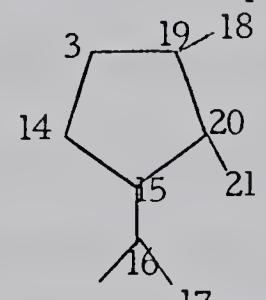
APPENDIX

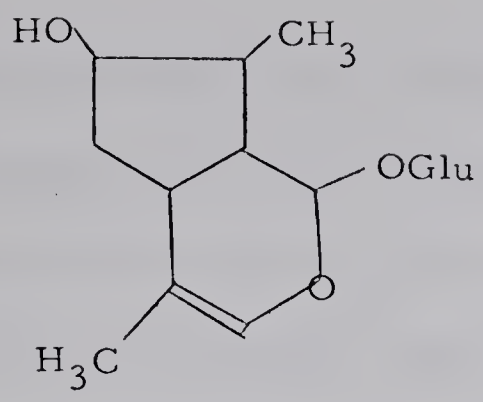
BIOSYNTHESIS OF INDOLE ALKALOIDS

It has been shown that tryptophan is a precursor in the biosynthesis of ajmaline.[37] However, the origin of the non-tryptophan derived portion has been the subject of much controversy. Woodward[9] and Robinson[38] suggested that C_3 and C_{14}-C_{20} were derived from 3,4-dihydrophenylalanine. Wenkert[39] proposed that these carbons were derived from prephenic acid, while Thomas[40] and Wenkert[41] proposed that these carbons were derived from a monoterpene having the carbon skeleton (116).



116

Leete and co-workers[42] proposed that three molecules of acetylcoenzyme A are involved in the formation of carbons 3, 14, 15, 18, 19 and 20. At C_{15} condensation takes place with malonylcoenzyme A to form carbons 16 and 17, while C_{21} is derived from formaldehyde or its biological equivalent.[44] Recently, Battersby and co-workers[45] reported that results from feeding experiments with sodium mevalonate and geraniol labelled at various positions strongly supported the cyclopentanoid monoterpene hypothesis.[46] Of the many cyclopentanoid monoterpenes which could serve as precursors of indole alkaloids, loganin (117) was considered by these authors to be the most probable one.[47] However, other possibilities are monotropeine methyl ester, verbenalin and genepin.



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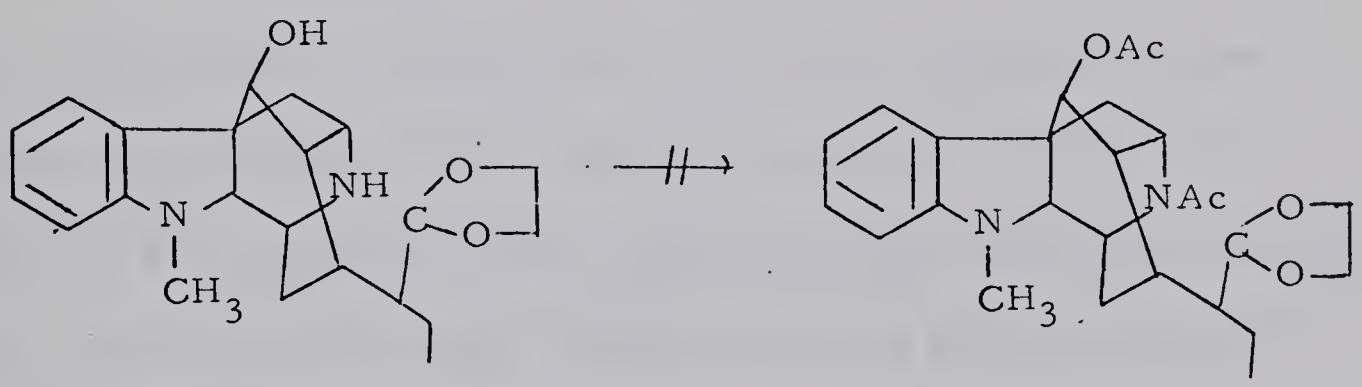
Separate feeding experiments with labelled verbenalin and monotropeine monoester into Vinca rosea plants were unsuccessful but when (O-methyl-^{3}H)loganin was fed into Vinca rosea plants, radioactive alkaloids, catharanthine, vindoline, perivine, serpentine and ajmalicine were isolated. Zeisel demethylation of catharanthine, serpentine and ajmalicine proved that all the radioactivity was located at the ester methyl group. These experiments strongly support that loganin is the most probable precursor of indole alkaloids and further experiments with multiple-labelled loganin are planned by these authors to prove the intact biological conversion of loganin system into indole alkaloids. Additional evidence for the above hypothesis is that loganin was found to be present in Vinca rosea plants.

AN ATTEMPT TO PREPARE AJMALINE KETAL 22

A solution of ajmaline 1 (1.63 g, 5 mmoles) in dry benzene (150 ml) containing ethylene glycol (5 ml) and p-toluenesulfonic acid (1.29 g, 7.5 mmoles) was refluxed overnight. After cooling, the solution was poured into 5% sodium bicarbonate solution (100 ml). The organic layer was separated and the aqueous layer extracted with several portions of ether. The combined extracts were washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated to give material with mp 145-152°; $\nu_{max}^{CHCl_3}$ 3580, 3300, 1601, 980, 950 cm^{-1}; nmr τ 2.55-3.55 (4H, aromatic), 5.7 (1H), 7.3 (3H, singlet), 6.5 (6H, quartet), 8.8 (3H, triplet).

The above product was acetylated as usual giving material whose infrared spectrum indicated the absence of -N-C=O absorption, thus

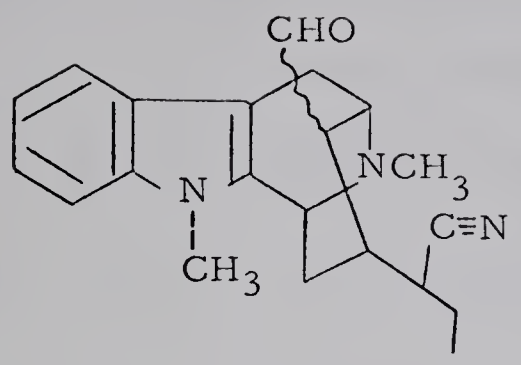


22 118

ruling out structure 118. No work was done to identify the structure of the product obtained by ketalization of ajmaline.

PREPARATION OF ANHYDRO-N_b-CARBOMETHOXYAJMALOL OXIME 46

At the earlier stage of the work it was thought that compound 46 could be used as a possible key intermediate and was prepared as shown in Scheme XII. Reduction of 27 with sodium borohydride afforded alcohol (43), the latter upon acetylation provided acetate (44). By carrying out a modified von Braun reaction of 44 with methyl chloroformate, one would expect the reagent to react with the tertiary nitrogen to break one C-N linkage and the carbomethoxy group would then become attached to the nitrogen. This was accomplished by allowing a solution of 44 in acetone containing large excess of methyl chloroformate to stand for 2 hours. This afforded a yield of 15% of the desired compound 45 after purification by chromatography. Prolonged standing did not increase the yield. In an effort to obtain better yield, the residue after each two-hour treatment, without chromatography was retreated with an excess of reagent. Progress of the reaction was followed by taking the infrared spectrum of each residue until a strong -NC=O absorption band was obtained. The final yield was 91%. Mild hydrolysis of 45 with sodium methoxide provided alcohol 46. Mild oxidation of 46 in DMSO containing DCC and pyridinium trifluoroacetate afforded aldehyde (47) in 70% yield after chromatography from alumina. Oxidation of 46 with DMSO containing an excess of acetic anhydride also afforded 47 in 70% yield. The latter method was preferred because of its simplicity. The infrared spectrum of 46 showed absorptions attributed to aldehyde (2700, 1725), nitrile (2230 cm^{-1}) and amide carbonyl (1695 cm^{-1}) and the nmr spectrum showed absorptions at



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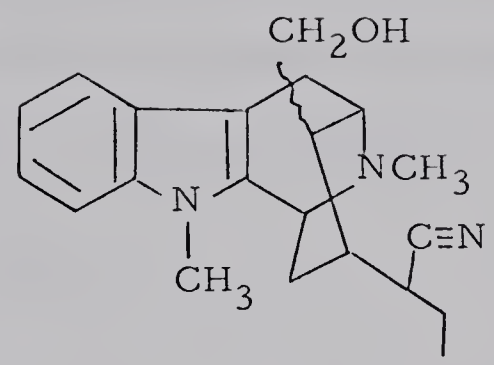

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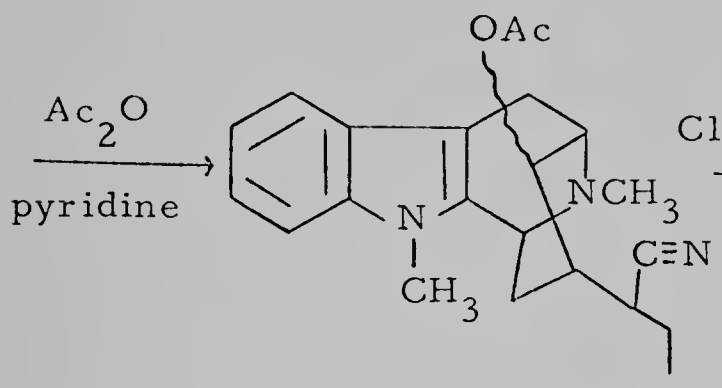

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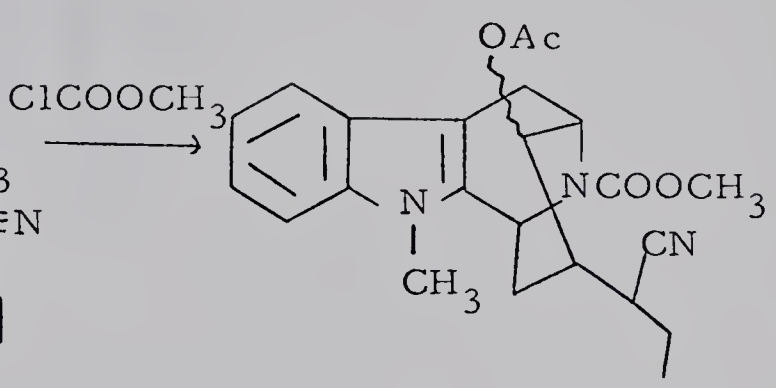

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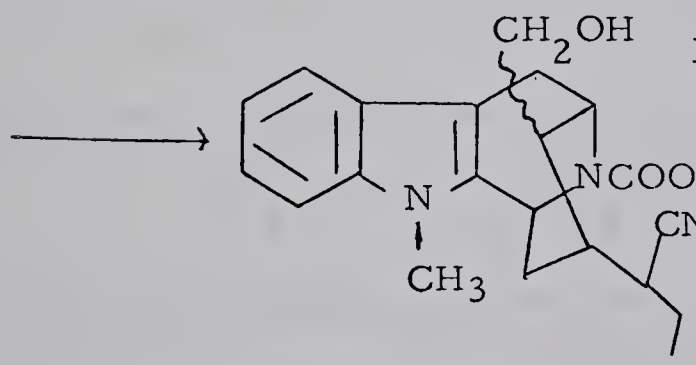

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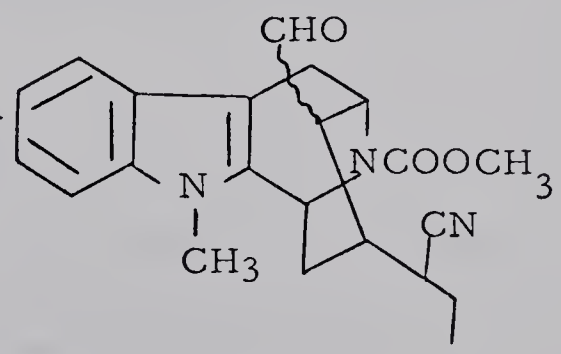

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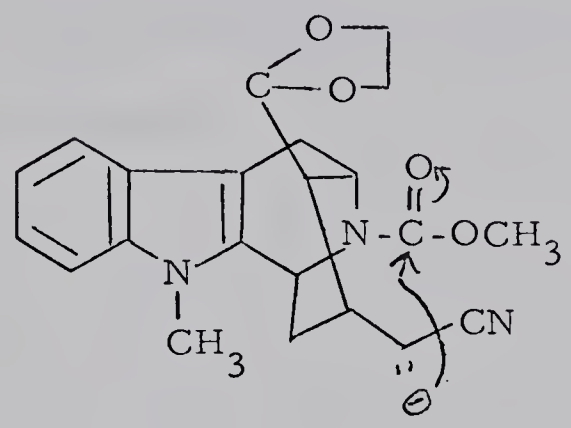
SCHEME XII

τ1.25 (singlet, C$\underline{H}$O), 6.32 (singlet, N_a-C$\underline{H}_3$), 6.25 (singlet, -OC$\underline{H}_3$).

However, compound 46 turned out to be an undesirable intermediate because at one step of the synthetic scheme wherein an ethyl group was introduced at C_{20}, cyclization was also effected under the reaction condition as shown in the structure below (117).



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NMR STUDY OF THE KEY INTERMEDIATE 19a

The interconversion frequency k (with simplifying assumption by Gutowsky) was obtained from the formula

$$k/\pi = \sqrt{(\delta^2 - \Delta^2)/2}$$

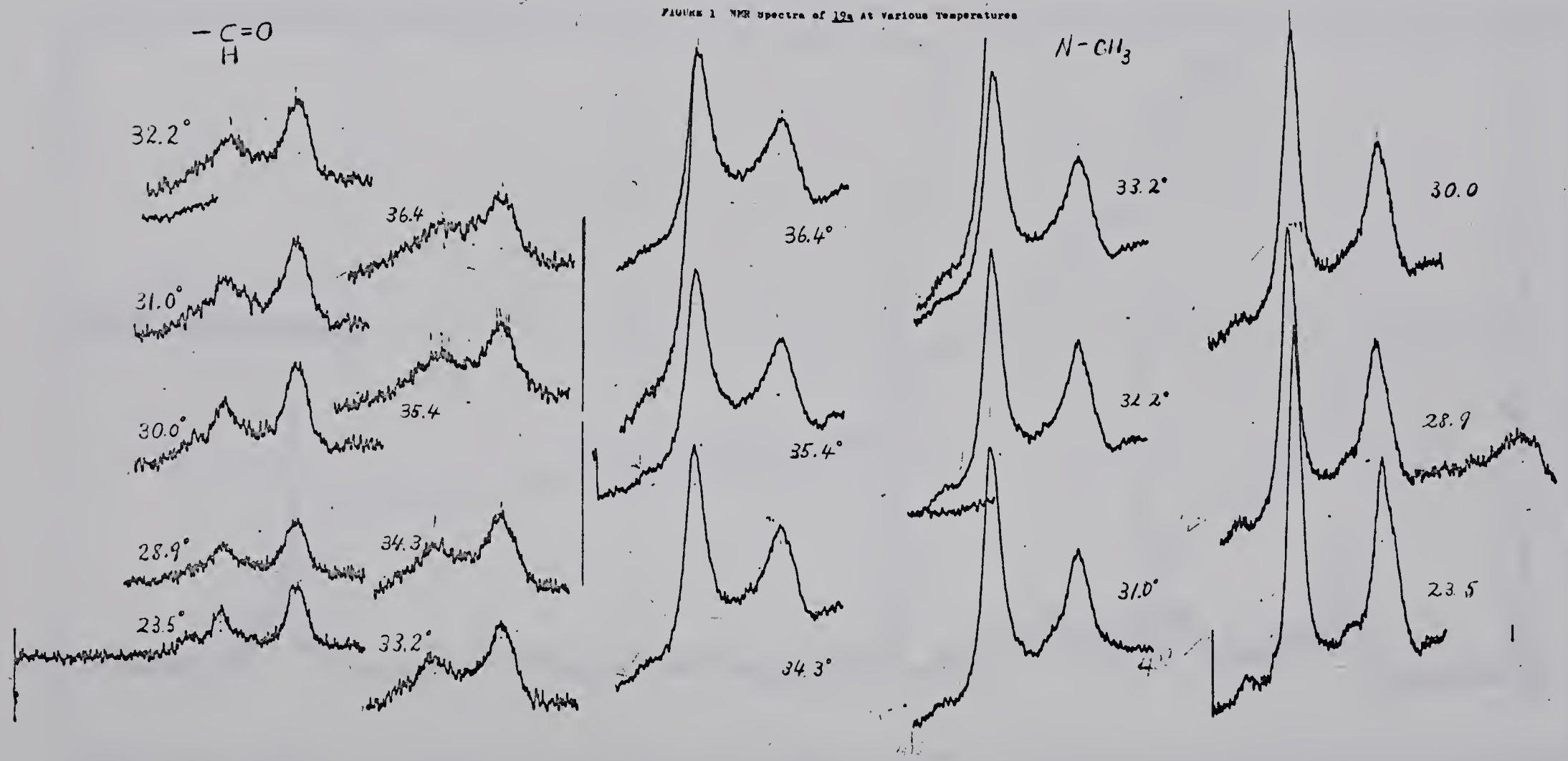
where Δ is the frequency separation between peak maxima and δ is the chemical shift between the two structures. A useful check on the validity of the above assumption was obtained by calculating α, the ratio of the intensity, taken midway between the peak maxima to the intensity, taken at peak maxima. The calculated α, given by the expression $1 - \Delta^4/\delta^4$, was compared to the observed values. Pertinent data are presented in Table I (page 33).

The Arrhenius energy E_a was determined from a plot of ln k vs 1/T over the temperature range 28.9 - 40.8°. The value for $\Delta H^{\ddagger}$ was obtained from $\Delta H^{\ddagger} = E_a - RT$. The entropy of activation $\Delta S^{\ddagger}$ was calculated from the Eyring rate equation

$$k = \kappa \ (K_b T/h) \exp(\Delta S^{\ddagger}/R - \Delta H^{\ddagger}/RT)$$

where κ is unity, K_b is Boltzman constant, h is Planck's constant and R is the universal gas constant.

FIGURE 1 NMR Spectra of 19a At Various Temperatures



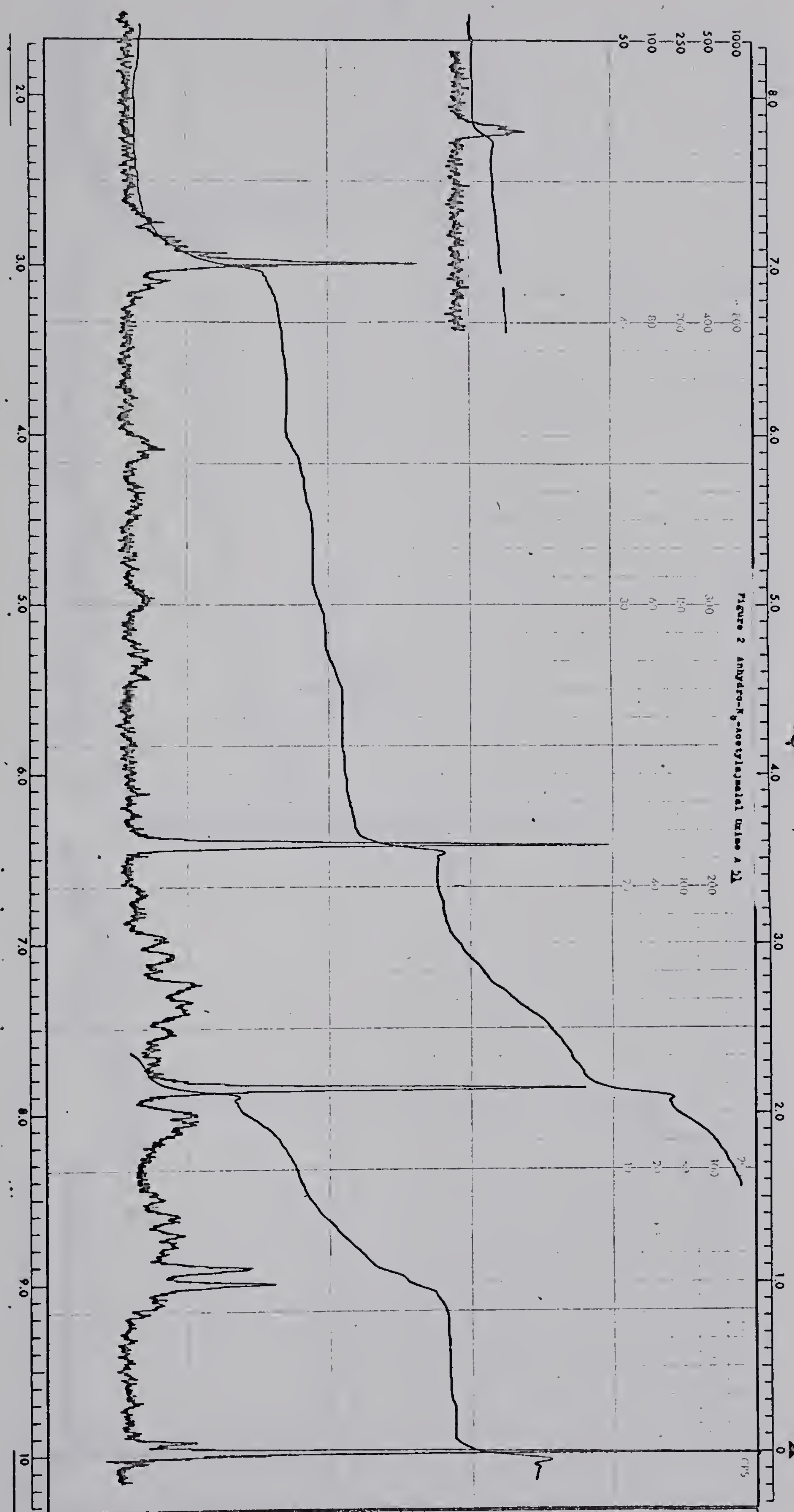
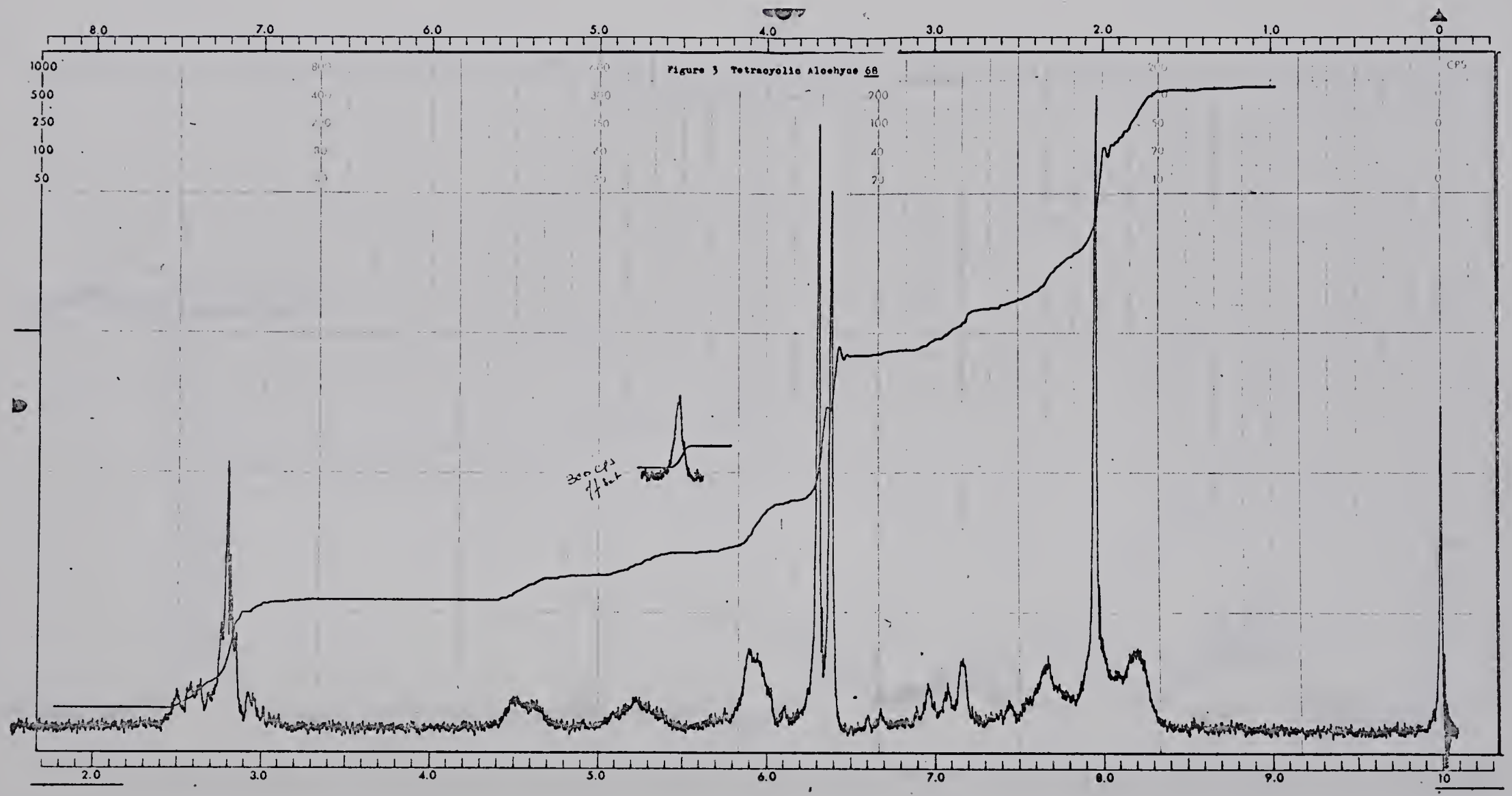


Figure 2 Anhydro-N_b-Acetylajmalol Oxime A 21

Figure 3 Tetracyclic Alcohyde 68



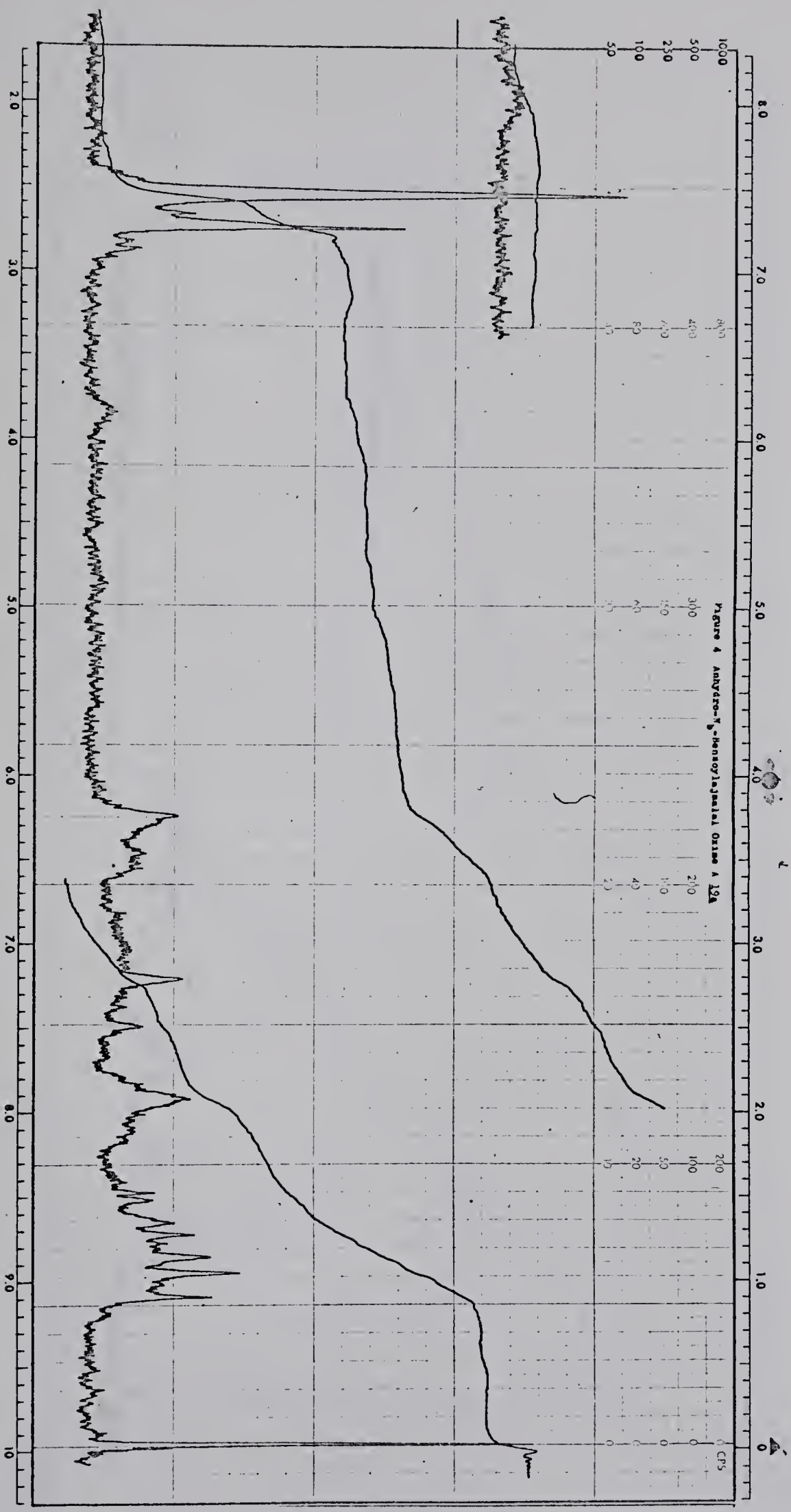


Figure 4 Anhydro-Tᵦ-Benzoylajmalol Oxime A 12a

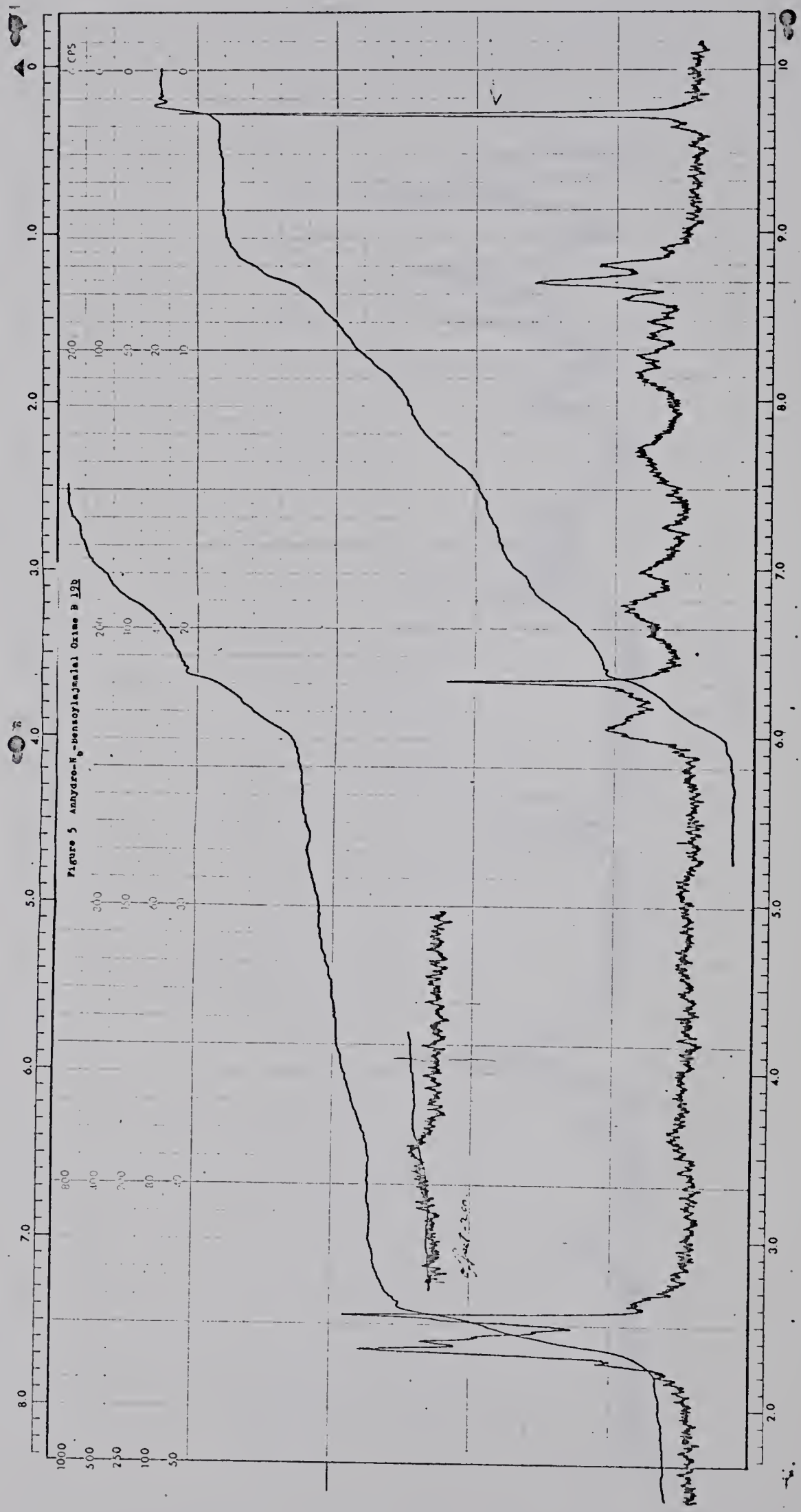
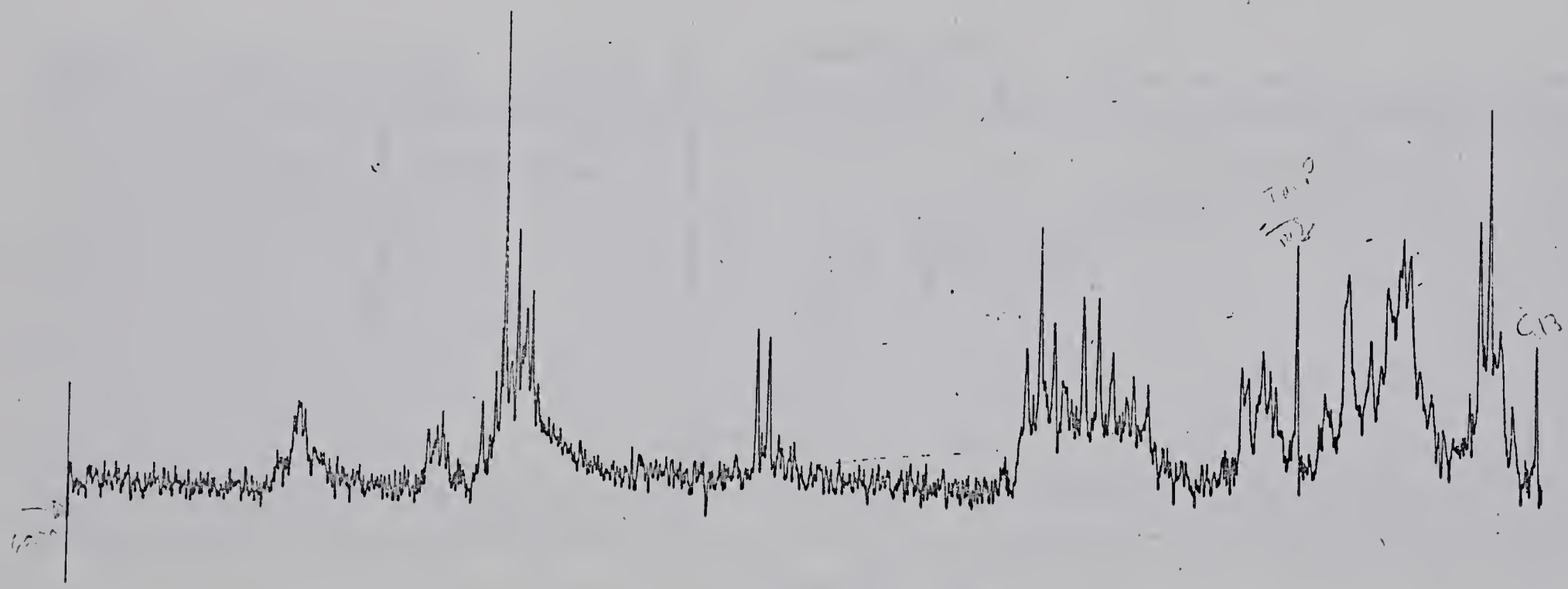
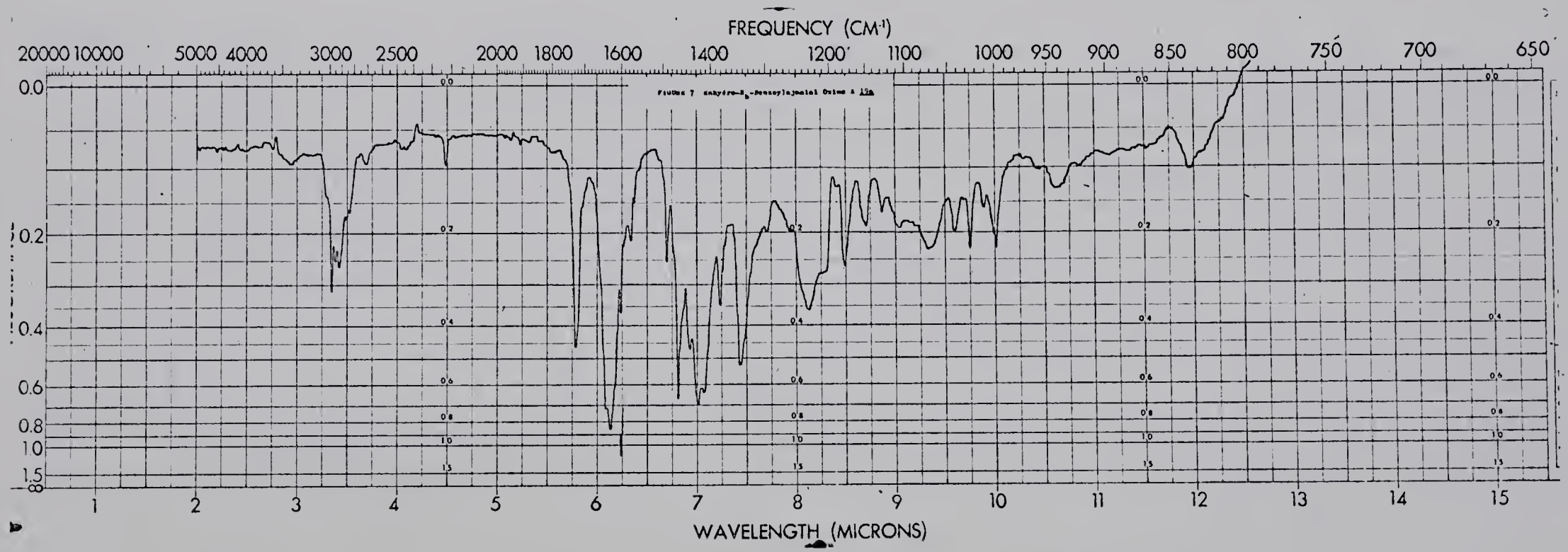


Figure 5 Anhydro-N$_6$-benzoyladenosine Oxime B 192

Figure 6 Compound 22




FREQUENCY (CM-1)
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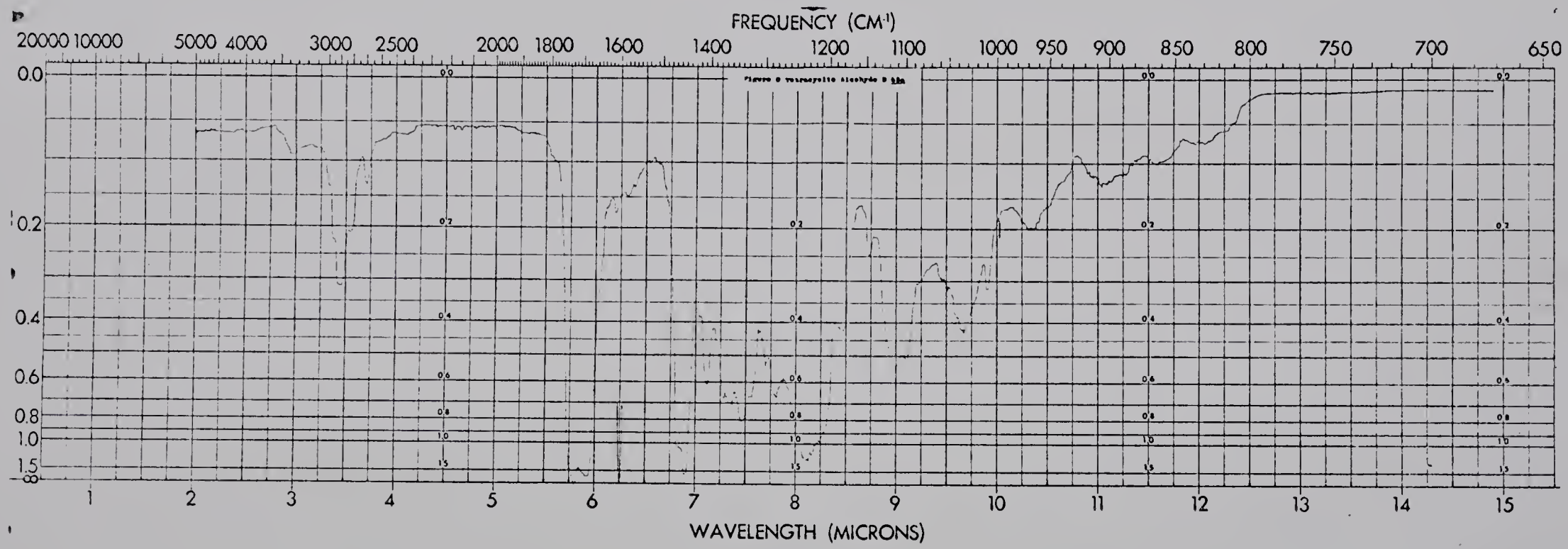
0.0
0.2
0.4
0.6
0.8
1.0
1.5
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


FREQUENCY (CM-1)
20000 10000 5000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700 650
0.0
0.2
0.4
0.6
0.8
1.0
1.5
∞
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)